National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Dutch Committee for Safety Assessment of Food Contact Materials

CBVV

Opinion

on an application for authorisation under the Dutch Commodities Act Decree on packaging and consumer articles for

Adipic acid dihydrazide

CAS Number: 1071-93-8

Submitting applicant: Covestro Netherlands B.V.

CBVV-S1033-D0045

Adopted

6 November 2023

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1. Introduction

Before a substance is authorised to be used in food contact materials (FCM) and is included in a positive list, an opinion on its safety is required. This is laid down in Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food[1], and implemented in the Dutch Commodities Act Decree on packaging and consumer articles (Warenwetbesluit verpakkingen en gebruiksartikelen)[2] and its corresponding Regulation (Warenwetregeling verpakkingen en gebruiksartikelen) [3]. In case industry seeks authorisation for a substance that is not yet on a positive list and which is used in a material for which so far no harmonized EU legislation applies, it may submit an application for authorisation to the Dutch Committee for Safety Assessment of Food Contact Materials (CBVV) for its evaluation. Such an application may also be submitted for a modification of a current entry on a positive list. The CBVV will carry out an assessment of the risks related to the intended use of the substance and deliver a scientific opinion.

In this case, the CBVV received an application from Covestro Netherlands B.V., requesting the evaluation of the substance adipic acid dihydrazide (CAS No 1071-93-8) for modification of its inclusion in Chapter X (Coatings), subsection a (monomers) of section 3 (Dispersions of macromolecular substances in water) of Part A of the Annex to the Commodities Act Regulation on packaging and consumer articles.

2. Data and methodologies

2.1 Data

The applicant has submitted a dossier in support of their application for the authorisation of adipic acid dihydrazide (ADH) to be used as a raw material in the production of water-based dispersions that will be used as the cohesive component (binders) for coatings/ primers. For the worst case situation that ADH may not have completely reacted in the coatings/primers, the applicant provided at the same time an additional dossier for ADH as additive. Since that however is not an intended use, the information in the 'ADH as additive' dossier will be considered in the present application for the intended use of ADH as monomer. Both dossiers have also been submitted to the Swiss authorities, for inclusion into Swiss Ordinance SR 817.023.21, Annex 10, Part A. Additional information was provided by the applicant during the assessment process in response to requests from the CBVV sent on 24 October 2022 and 17 March 2023 (see 'Documentation provided to CBVV').

Data submitted and used for the evaluation are:

Non-toxicological data
- Data on chemical identity
- Data on purity and impurities
- Data on physical and chemical properties

[1] Regulation (EC) No 1935/2004 of the European parliament and of the council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC. OJ L 338, 13.11.2004, p. 4-17.

[2] Besluit van 30 mei 2005, houdende vaststelling van het Warenwetbesluit verpakkingen en gebruiksartikelen in verband met Verordening (EG) nr. 1935/2004 van het Europees Parlement en de Raad van de Europese Unie van 27 oktober 2004 inzake materialen en voorwerpen bestemd om met levensmiddelen in contact te komen en houdende intrekking van de richtlijnen 80/590/EEG en 89/109/EEG (PbEU L 338) (Warenwetbesluit verpakkingen en gebruiksartikelen). Staatsblad van het Koninkrijk der Nederlanden, 2005, 420.

[3] Regeling van de Minister van Volksgezondheid, Welzijn [en Sport] van 14 maart 2014, kenmerk 328583-117560-VGP, houdende vaststelling van de Warenwetregeling verpakkingen en gebruiksartikelen die in contact komen met levensmiddelen (Warenwetregeling verpakkingen en gebruiksartikelen). Staatscourant, 2014, 8531.

- Data on intended use and existing authorisation(s)
- Data on the manufacturing process of the substance/FCM
- Data on residual content of the substance
- Data on the potential migration of the substance

Toxicological data
- Bacterial gene mutation test
- In vitro mammalian cell micronucleus test
- 90-day oral toxicity study in rats
- Reasoning for absence of bio-accumulative potential in man
- QSAR analysis for oligomers

2.2 Methodologies

The assessment was conducted in line with the principles laid down in Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food. This Regulation underlines that applicants may consult the Guidelines of the Scientific Committee on Food (SCF) for the presentation of an application for safety assessment of a substance to be used in FCM prior to its authorisation (European Commission, 2001), including the corresponding data requirements. The dossier that the applicant submitted for evaluation was in line with the SCF guidelines (European Commission, 2001) and the Note for Guidance of the European Food Safety Authority (EFSA) for the preparation of an application for the safety assessment of a substance to be used in plastic FCM (EFSA CEF Panel, 2021).

The methodology is based on the characterisation of the substance that is the subject of the request for safety assessment prior to authorisation, its impurities and reaction and degradation products, the evaluation of the exposure to those substances through migration and the definition of minimum sets of toxicity data required for safety assessment.

To establish the safety from ingestion of migrating substances, the toxicological data indicating the potential hazard and the likely human exposure data need to be combined. Exposure is estimated from studies on migration into food or food simulants and considering that a person may consume daily up to 1 kg of food in contact with the relevant FCM.

As a general rule, the greater the exposure through migration, the more toxicological data is required for the safety assessment of a substance. Currently there are three tiers with different thresholds triggering the need for more toxicological information as follows:

a) In case of high migration (i.e. 5–60 mg/kg food), an extensive data set is needed.
b) In case of migration between 0.05 and 5 mg/kg food, a reduced data set may suffice.
c) In case of low migration (i.e. < 0.05 mg/kg food), only a limited data set is needed.

More detailed information on the required data is available in the SCF guidelines (European Commission, 2001) and the EFSA Scientific Committee recommendations on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011).

3. Assessment

The substance ADH has previously been evaluated by EFSA, who expressed a scientific opinion on the safety of its use as a crosslinker for acrylic polymers with keto side groups for non-self-supporting coatings on polyolefins and adhesives in laminates made from plastics (EFSA CEF Panel, 2015). Since coatings are not covered by EU legislation, the G4 Commission (the predecessor of the CBVV) adopted EFSA's opinion on this limited claim of intended use without re-assessment when it in 2016 received a dossier from BASF Nederland B.V. for the same application. This resulted in the following entry in Chapter X, section 3, subsection a of Part A of the Annex to the Commodities Act Regulation on packaging and consumer articles[4]:

> adipic acid dihydrazide; CAS No 1071-93-8; SML = 0.05 mg/kg; only to be used as crosslinker in acrylic copolymers with keto side groups, in coatings on plastics and not in direct contact with food.

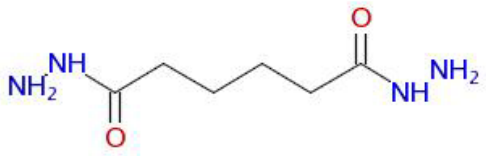
According to the applicant, it is the purpose of the present application to extend the application of ADH as crosslinker to react with any ketone groups in a polymer structure, for example an acrylic or polyurethane dispersion. Furthermore, the intended application is not limited to plastic material but covers also non-plastic materials (such as aluminium, paper and board), and for plastic materials the use is not limited to polyolefins only. The proposed SML is 5 mg/kg. The packaging materials coated/printed with ADH containing binders are intended for all food types for both indirect and direct food contact applications, with both single and repeated use applications in scope. Contact times with foodstuffs can range from several minutes (paper and board) to more than 6 months (for products with a long shelf life). These packaging materials are not intended to be used for oven applications, but microwave heating of foodstuffs with a maximum of 100°C is possible.

3.1 Non-toxicological data

3.1.1 Identity of the substance

Molecular formula: $C_6H_{14}N_4O_2$

Structural formula:



ADH is a raw material to produce self-crosslinking water-based dispersions that are used as the cohesive component (binder) for coatings and inks. In the preparation of binders, ADH can be added to a polymer dispersion, as an in-situ crosslinking agent reacting with specific functional groups (keto-functionality) which are incorporated in the polymer during synthesis. ADH is a crosslinker with two hydrazide moieties, each of which can react with ketone groups present on polymers present in the binder. Such polymers are typically linear (meth)acrylic (styrene) copolymers with pendant ketone groups introduced using diacetone acrylamide (DAAM) or acetoacetoxy ethylmethacrylate (AAEM), but may also be

[4] Regeling van de Minister van Volksgezondheid, Welzijn en Sport van 26 april 2022, 3348384-1027396-VGP, houdende wijziging van de Warenwetregeling verpakkingen en gebruiksartikelen in verband met het verwijderen en toevoegen van stoffen aan deel A van de bijlage en enkele technische wijzigingen. Staatscourant, 2022, 11934.

ketone-functional polyurethane, alkyd or other polymers. The self-crosslinking units in the polymer result in a dense crosslinked network that has improved functional properties as compared to non-crosslinked systems.

3.1.2 Physical and chemical properties

Melting point: 181°C

Boiling point and decomposition temperature: 206 °C

Water solubility: 102 ± 2 g/L at 20 °C
ADH is largely hydrophilic. Therefore, the substance will be good soluble in the simulants water/ethanol and water/acetic acid and limited soluble in the simulants iso-octane and olive oil.

The log Ko/w (octanol/water partition coefficient) of ADH varies from –2,1 to –2,7, depending on the source of information.

ADH is neutral/mildly basic. In the presence of suitable reagents, ADH as monomer will intentionally transform in the reaction with isocyanate functionality forming an aminourea group. Typical reaction/application conditions for ADH are T<100°C (boiling point of water).

Hydrolytic stability studies of ADH under various pH-conditions showed safe use conditions for FCM applications where ADH is either in direct or indirect contact with hydrophilic and acidic foods (with pH ≥ 4.5) and where ADH is in indirect contact with acidic food (pH < 4.5). In case of direct food contact with very acidic food (pH 3-4), however, hydrolytic decomposition of ADH might occur under very specific temperature and time conditions. In order to guarantee safe levels of potential breakdown products under such severe conditions, a restriction is therefore recommended in the dossier for the ‘direct contact with acidic food’ scenario that customers assess the hydrolytic stability of ADH under pH, temperature and time conditions of the final application. The CBVV considers a restriction fit for this scenario, but in more strict terms (see section 4) than the suggested recommendation.

3.1.3 Migration data

In the migration assessment, residual ADH, ADH-containing oligomers with a molecular weight < 1000 Da, and impurities in ADH were identified as potential migratable substances. The maximum migration of these substances from a typical ADH containing product was determined based on worst-case migration calculations and, for the oligomers, also on migration modelling. For residual ADH and the impurities hydrazine and 6-hydrazinyl-6-oxohexanoic acid this resulted in worst case migrations of 0.20 ppm, 0.037 ppb and 0.036 ppm, respectively. So, well below their proposed safe levels of 5 ppm, 2.7 ppb and 5 ppm, respectively. Even in case ADH may not have completely reacted in a coating, the migration of these substances was demonstrated to be below their respective SMLs.

Following extraction in 10% ethanol, the ADH-functional oligomers present in the polymer system were quantified by LC-MS. The resulting concentrations were used as input for the migration assessment by worst-case calculations and by modelling with Migratest©EXP. The worst-case migration as determined by calculation was 308 ppb. This was considered an overestimation, as these oligomer compounds have a relatively high molecular weight. Therefore, a theoretical modelling approach was also applied, using the theoretic worst-case substrate thicknesses (12 micron for BOPP or PE film) and the worst-case substrate thicknesses in practice (28 micron for BOPP and 50 micron for PE). For the theoretical situation, this resulted in a migration of up to 60 ppb, whereas for the practical situations

migration was below 30 ppb. So, in both situations the migration is well below the proposed safe threshold of 90 ppb.

3.2 Toxicological data

3.2.1 Genotoxicity

3.2.1.1 Bacterial reverse mutation test

ADH was tested in two bacterial reverse mutation tests (one with Salmonella typhimurium strains TA1537, TA1535, TA98, TA100 and with Escherichia coli WP2 uvrA, the other with Salmonella typhimurium strains TA1535, TA98, TA100, TA102 and TA97a), both performed with and without metabolic activation and both in accordance with OECD TG 471. No substantial increases in revertant colony numbers over control counts were obtained with any of the tester strains following exposure to ADH at any concentration up to and including 5000 µg/plate in either the presence or absence of S9 mix. ADH thus did not show evidence of mutagenic activity under the test conditions used.

3.2.1.2 In vitro mammalian cell micronucleus assay

ADH was also tested in an in vitro micronucleus test in cultured peripheral human lymphocytes. The test was conducted in accordance with OECD TG 487. No relevant increase in the number of binucleated cells with micronuclei was observed at concentrations up to and including 1742 µg/mL (0.01 M) in the absence and presence of S9-mix. Under the experimental conditions used, ADH was considered not clastogenic or aneugenic.

3.2.1.3 Other information

Reference was made to the earlier EFSA opinion on the safety assessment of adipic acid dihydrazide for use in food contact materials (EFSA, 2015). In this opinion, EFSA concluded that based on the evidence available from in vitro and in vivo tests (five bacterial reverse mutation tests, an in vitro gene mutation test in mouse lymphoma cells, and two in vivo mouse bone marrow micronucleus tests) ADH is not considered genotoxic.

3.2.2 General toxicity

3.2.2.1 Repeated dose 90-day oral toxicity study

ADH was tested in an 90-day oral toxicity study, in which rats were given daily doses of 0, 100, 300 or 1000 mg ADH/kg bw by gavage. The study was performed in accordance with OECD TG 408. Adverse treatment-related effects were identified in the brain (vacuolation) and sciatic nerve (demyelination) at 1000 mg/kg bw per day, and in the liver (histopathological changes in combination with changes in clinical liver parameters and increased liver weight) at 300 and/or 1000 mg/kg bw per day. The NOAEL in this study was 100 mg/kg bw per day, based on increased incidence and severity of single cell necrosis observed in the liver of male rats at 300 mg/kg bw per day.

3.2.2.2 Accumulation in man

ADH has a very low log Ko/w (< -2). Given that a log Ko/w value below 3 is considered sufficient evidence for the lack of accumulative potential in the mammalian body, ADH is not expected to accumulate in humans.

3.2.3 Toxicity data on oligomers

For the ADH-functional oligomer material identified in polymer dispersions after use of ADH as crosslinker, no toxicity data are available. The dossier however contains a QSAR analysis in which all oligomer structures were classified in Cramer class III. For most structures, the repeated dose toxicity alert and in vivo mutagenicity alert are the same as for ADH. The genotoxicity alert could be discarded, as ADH is not considered a genotoxic

substance, based on experimental data. The same repeated dose toxicity alert underlines the same potential toxicological profile for these structures as for ADH. The alert related to the carbamate groups, present in some of the oligomers found, was also discarded based on the rationale that acetylcholinesterase inhibition is only seen in carbamates that have the carbamate group at the end of the structure, with the nitrogen alkylated by a small (methyl) group. In contrast, in those ADH oligomers containing a carbamate group, this group is present in the central part of the structure and or surrounded by groups creating a steric hindrance which will not allow a proper interaction with the catalytical site of the enzyme, needed to show anticholinergic activity.

As all oligomer structures were classified as Cramer class III, a TTC of 90 µg/person per day applies (EFSA, 2019). Hence, a group restriction of 90 µg/kg food for the migration can be used in the risk assessment of the oligomers.

3.2.4 Toxicity of the impurities

Two impurities were identified in ADH, being hydrazine (CAS 302-01-2) and 6-hydrazinyl-6-oxohexanoic acid (CAS 6292-67-7). In the dossier SMLs have been derived for both substances. For hydrazine, a CMR substance due to its classification as Carc. 1B, publicly available assessments were used. Assuming genotoxicity of hydrazine and using the Virtually Safe Dose approach from a TD50 value from an oral study in rats, an SML of 2.7 µg/kg for hydrazine was derived. For 6-hydrazinyl-6-oxohexanoic acid, a QSAR-approach and read across from ADH were used to derive an SML of 5 mg/kg. Both self-derived SMLs are considered conservative in nature, given for instance that EFSA considered for hydrazine 0.028 ppm a safe limit in the review of maleic hydrazide as pesticide (EFSA, 2016).

The CBVV considered the appropriateness of a sum-SML for 6-hydrazinyl-6-oxohexanoic acid and ADH, given their similar toxicity. However, as the contribution of 6-hydrazinyl-6-oxohexanoic acid to this sum is very limited a sum-SML was not considered necessary.

3.2.5 Concluding remarks on toxicity

ADH is considered to be not genotoxic nor to have bioaccumative potential in humans. A repeated dose 90-day oral toxicity study in rats with a derived NOAEL of 100 mg/kg bw per day is available. This NOAEL is sufficient to allow for an SML of 5 mg/kg food, i.e. the highest SML that can be set with the dataset available.

The oligomers identified were all classified as Cramer class III, for which a TTC of 90 µg/person per day applies. A group restriction of 90 µg/kg food for the migration of oligomers can be used in the risk assessment. For the impurities, the self-derived SMLs can be used in the risk assessment.

4. Conclusions

Based on the data submitted, the CBVV concluded that, aside from one use scenario, the substance adipic acid dihydrazide does not raise a safety concern for the consumer under the intended and tested conditions of use as a monomer in coatings. The particular scenario concerns the use of ADH in coatings that are in direct contact with very acidic food, potentially resulting in the hydrolytic stability of ADH being insufficient to guarantee safety. To CBVV's opinion, the current entry for the substance in part A of the Annex to the Commodities Act Regulation on packaging and consumer articles (see section 3) can be changed as follows:

Chapter	Section	Subsection
X. Coatings	3. Dispersions of macromolecular substances in water	a. monomers

CAS No	Name	SML mg/kg	Restrictions and specifications
1071-93-8	Adipic acid dihydrazide	5	Not to be used in coatings in direct contact with acidic food

In Dutch:

Hoofdstuk	Paragraaf	Subparagraaf
X. Deklagen	3. Dispersies van macromoleculaire stoffen in water	a. monomeren

CAS Nr	Naam	SML mg/kg	Restricties en specificaties
1071-93-8	adipinezuur dihydrazide	5	Niet te gebruiken in deklagen in direct contact met zure voedingsmiddelen

Documentation provided to CBVV

1) Initial dossier. June 2022. Submitted by Covestro Netherlands B.V.
2) Additional data. December 2022/February 2023. Submitted by Covestro Netherlands B.V.
3) Additional data. August/October 2023. Submitted by Covestro Netherlands B.V.

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Abbreviations

BOPP	biaxially-oriented polypropylene
bw	body weight
CAS	chemical abstracts service
CMR	carcinogenic, mutagenic, reproductive toxic
EFSA	European Food Safety Authority
FCM	food contact materials
Ko/w	n-octanol/water partition coefficient
LC-MS	liquid chromatography, mass spectrometry
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PE	polyethylene
QSAR	quantitative structure-activity relationship
TTC	Threshold of Toxicological Concern
SCF	Scientific Committee on Food
SML	specific migration limit
TD50	chronic dose-rate in mg/kg bw per day which would induce tumours in half the test animals at the end of a standard lifespan for the species
TG	test guideline