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

Hexane, 1,6-diisocyanato-, homopolymer, Bu glycidyl ether- and polyethylene glycol mono-Me ether-blocked, reaction products with propylenimine

CAS Number: 2416007-57-1

Submitting applicant: Covestro Coating Resins BV

CBVV-S1032-D0044

Adopted

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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 Coating Resins BV, requesting the evaluation of the substance 'hexane, 1,6-diisocyanato-, homopolymer, Bu glycidyl ether- and polyethylene glycol mono-Me ether-blocked, reaction products with propylenimine' (CAS No 2416007-57-1) for inclusion in Chapter X (Coatings) of Part A of the Annex to the Commodities Act Regulation on packaging and consumer articles, in the following (sub)sections:

- section 3 (Dispersions of macromolecular substances in water), subsections 3a (monomers) and 3m (other substances);
- section 7 (Solutions in organic solvents), subsection 7c (macromolecular compounds).

2. Data and methodologies

2.1 Data

The applicant has submitted a dossier in support of their application for the authorisation of the polymeric aziridine 'hexane, 1,6-diisocyanato-, homopolymer, Bu glycidyl ether- and polyethylene glycol mono-Me ether-blocked, reaction products with propylenimine' (NeoAdd PAX) to be used as crosslinker in the production of coatings. This dossier has also been submitted to the Swiss and German authorities, for inclusion into Swiss Ordinance SR 817.023.21, Annex 10, Part A and the German Printing Ink Ordinance, respectively. Additional information was provided by the applicant during the assessment process in response to requests from the CBVV sent on 15 June 2022 (see 'Documentation provided to CBVV').

[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 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
- 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 tests
- In vitro mammalian cell micronucleus test
- In vitro acetylcholinesterase inhibition test
- Other information

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 has not been evaluated in the past by the SCF or EFSA, and it is not listed in the Dutch Commodities Act Regulation on packaging and consumer articles. Japan allows the use in non-food contact layers, provided that the migration at the intended use conditions stays below 10 ppb.

The purpose of the present application is to get authorisation for the use of the NeoAdd PAX crosslinker as an ingredient in coating formulations intended to react with the carboxylic acid functionality of water-based resins to form an overall crosslinked composition. After having reacted, the crosslinker will be part of the polymeric backbone. The crosslinker compounds are synthesized in solvent for use in water-based dispersions (i.e., emulsions) that will be used as binders. These binders are present in primers, printing inks, overprint varnishes and coatings applied onto various substrates used for food packaging applications. NeoAdd PAX is intended to be used in both direct and indirect contact with food for all food types. Contact times with foodstuffs can range from several minutes to more than 6 months (for products with a long shelf life). The packaging materials coated/printed with NeoAdd PAX crosslinker are not intended to be used for oven applications, but microwave heating of foodstuffs with a maximum of 100°C is possible. The specific migration limit (SML) proposed is 0,05 mg/kg (50 ppb).

3.1 Non-toxicological data

3.1.1 Identity of the substance

The FCM NeoAdd PAX is a multifunctional polymeric aziridine crosslinker, made according to a proprietary synthetic process. Three NeoAdd PAX grades exist that contain crosslinkers described by the CAS number 2416007-57-1.

The FCM is typically marketed in 20-50% (w/w) solvent. Trade names are NeoAdd PAX-521 (80% FCM in ethyl acetate), NeoAdd PAX-523 (80% FCM in methoxy propyl acetate) and NeoAdd PAX-524 (50% FCM in dipropylene glycol dimethylether).

3.1.2 Physical and chemical properties

The NeoAdd PAX FCM is a slightly basic, yellow-brown viscous liquid (delivered in 20-50% solvent), with a molecular mass generally ranging from 1.1-10 kDa. The predicted water solubility and vapor pressure are very low. The predicted log Kow (octanol/water partition coefficient) ranges from 2.41-10.71. The viscosity is 1000-8000 mPa.s for NeoAdd PAX 521 and 523, and 20-500 mPa.s for NeoAdd PAX 524.

The decomposition temperature of the FCM is above 180°C and it will cure under acidic conditions one. It is insoluble in water and soluble in most organic solvents. After 4 hours in gastric juice simulant about 50-60% of the FCM is decomposed by single defined hydrolysis pathway leading to ring-opened aziridine crosslinker structures.

The FCM is intended to react with the carboxylic acid functionality of water-based resins to form an overall crosslinked composition. As it becomes part of an overall crosslinked coating, it is not expected to have specific interactions with any of the food simulants.

3.1.3 Migration data

Migration was assessed by worst-case calculations, assuming for each migratable substance 100% migration of its residual level in the dry coating layer. Migratable substances identified included 1) crosslinker structures, 2) residual raw materials (including their NIAS), 3) reactive intermediate and reactive side-products, 4) non-reactive side-products, and 5) reactive intermediate and side-products reacted to low-molecular weight binder components. In order to quantify the residual concentration of the crosslinker structures and the reactive intermediate and reactive side-products in the dry coating, extraction experiments were performed with three representative commercial production batches of NeoAdd PAX-521, 523 and 524, in both ethanol and chloroform, following preparation on (inert) aluminium sheets.

Based on worst-case migration calculations, it was shown that the migration of all identified migratable substances was below their safe thresholds. These were 50 ppb for group 1, 0.15-1800 ppb for group 2, 0.15 ppb for groups 3 and 5, and 90 ppb for group 4.

3.2 Toxicological data

3.2.1 Genotoxicity

3.2.1.1 Bacterial reverse mutation test

NeoAdd PAX was tested in two bacterial reverse mutation tests with four Salmonella typhimurium strains (TA98, TA100, TA1535 and TA1537) and Escherichia coli strain WP2uvrA, with and without metabolic activation. One test concerned NeoAdd PAX-521, the other the solvent-free version of NeoAdd PAX-524. Both tests were conducted in accordance with OECD TG 471 and used the plate incorporation method for the first experiment and the pre-incubation method for the second experiment. With the solvent-free version of NeoAdd PAX-524, no substantial increases in revertant colony numbers over control counts were obtained with any of the tester strains at any concentration up to and including 5000 µg/plate in either the presence or absence of S9 mix. For NeoAdd PAX-521 the results were identical, albeit that in the second experiment the top concentration had to be lowered to 2500 µg/plate due to precipitation occurring at the highest doses in the first experiment. It can be concluded that NeoAdd PAX did not show evidence of mutagenic activity under the test conditions used.

3.2.1.2 In vitro mammalian cell micronucleus assay

NeoAdd PAX-521 was also tested in an in vitro micronucleus test in cultured peripheral human lymphocytes. The test was conducted in accordance with OECD TG 487. In the first experiment, where the test item was tested up to 50 µg/mL for a 3 hour exposure time with a 27 hour harvest time in the absence and presence of metabolic activation, statistically significant increases in both the number of micronucleated mono- and binucleated cells were observed at the lowest or mid dose level, but not the high dose level. No such increases were observed in the second experiment, where the test item was tested up to 40 µg/mL (due to precipitation at 50 µg/mL) for a 24 hour exposure time with a 24 hour harvest time in the absence of metabolic activation. Given that the observed increases were within historical control data ranges and not dose related, they can be

considered not biologically relevant. It can be concluded that NeoAdd PAX was not clastogenic or aneugenic under the experimental conditions used.

3.2.1.3 Other information

Solvent-free versions of NeoAdd PAX-521/523 and NeoAdd PAX-524 were tested in the in vitro ToxTracker assay, in both the absence and presence of metabolic activation. ToxTracker is a panel of mammalian stem cell lines that contain different fluorescent reporters for induction of DNA damage, oxidative stress and protein damage. The test items did not activate either of the two genotoxicity markers and were thus in the test reports concluded to be not genotoxic. As the ToxTracker assay is still under validation by OECD, the results can only be considered supportive.

Ring-opened aziridine crosslinker structures are decomposition products of NeoAdd PAX, which are formed by hydrolysis when FCM is in contact with gastric juice simulant. QSAR analysis on the hydrolyzed crosslinker structures was compared with the QSAR results from the non-hydrolyzed crosslinker structures. Non-genotoxicity can be inferred for both the FCM in NeoAdd PAX and its hydrolysis products. This is supported by results obtained by investigation of genotoxicity using the ToxTracker assay.

3.2.2 General toxicity

3.2.2.1 Neurotoxicity

NeoAdd PAX contains carbamate moieties, a functional group often associated with acetylcholinesterase (AChE) inhibition and consequently neurotoxicity. Hence, NeoAdd PAX-523 was tested in an in vitro AChE inhibition test, using recombinant (pure) human AChE enzyme. Test concentrations ranged from 0.4-200 µg/mL. The test showed no AChE inhibition up to 0.8 µg/mL and only a very low level of AChE inhibition at 1.6 µg/mL. From there onwards, AChE inhibition dose-relatedly increased up to approximately 70% at 200 µg/mL. The IC_{50} value (i.e. the concentration of the test item needed to inhibit the AChE enzyme by 50%) was 25 µg/mL.

In the dossier, the risk of neurotoxicity caused by migration up to the proposed SML of 50 ppb was considered negligible, in view of the following:

- Absence of AChE inhibition up to and including 0.8 µg/mL (800 ppb) in the in vitro test.
- Gastrointestinal absorption is negligible, given the high molecular weight of NeoAdd PAX (> 1000 g/mol). It is therefore unlikely that it will reach the AChE in the human body in sufficient concentration to cause enzyme inhibition in vivo.
- Because of the bulkiness of its structure, it is to be expected that NeoAdd PAX cannot properly accommodate in the enzyme pocket of AChE. Consequently, the affinity of NeoAdd PAX for AChE will be very low.

3.2.2.2 Toxicity of migratable substances

In the dossier SMLs have been derived for all identified migratable substances, either by applying the TTC approach or using QSAR approaches. This results in SMLs that can be used in the risk assessment.

3.2.2.3 Accumulation in man

Based on the predicted log Kow (2.41-10.71), a certain degree of accumulation cannot be excluded. However, given the very low probability of oral uptake, accumulation is unlikely.

3.2.3 Concluding remarks on toxicity

As migration of NeoAdd PAX was shown to be below 50 ppb, the toxicological data provided in the dossier fulfil the requirements for a substance with low migration (i.e. < 0.05 mg/kg food). Based on the available data, NeoAdd PAX is concluded to be a non-genotoxic substance, and neurotoxicity in vivo is not to be expected. The self-derived SMLs for the identified migratable substances can be used in the risk assessment.

4. Conclusions

Based on the data submitted, the CBVV concluded that the polymeric aziridine 'hexane, 1,6-diisocyanato-, homopolymer, Bu glycidyl ether- and polyethylene glycol mono-Me ether-blocked, reaction products with propylenimine' does not raise a safety concern for the consumer under the intended and tested conditions of use as crosslinker in the production of coatings. To CBVV's opinion, the substance can be included in part A of the Annex to the Commodities Act Regulation on packaging and consumer articles as indicated in the tables below. The request of the applicant for inclusion also in subsection m (other substances) of section 3 in Chapter X is considered superfluous by the CBVV.

Chapter	Section	Subsection
X. Coatings	3. Dispersions of macromolecular substances in water 7. Solutions in organic solvents	a. monomers c. macromolecular compounds

CAS No	Name	SML mg/kg	Restrictions and specifications
2416007-57-1	Hexane, 1,6-diisocyanato-, homopolymer, Bu glycidyl ether- and polyethylene glycol mono-Me ether-blocked, reaction products with propylenimine	0.05	

In Dutch:

Hoofdstuk	Paragraaf	Subparagraaf
X. Deklagen	3. Dispersies van macromoleculaire stoffen in water 7. Oplossingen in organische oplosmiddelen	a. monomeren c. macromoleculaire verbindingen

CAS Nr	Naam	SML mg/kg	Restricties en specificaties
2416007-57-1	Reactieproducten van propyleenimine met 1,6-diisocyanato-hexaan homopolymeer, geblokkeerd met butylglycidylether en monomethoxy polyethyleenglycol	0,05	

Documentation provided to CBVV

1) Initial dossier. October 2021, with update in February 2022. Submitted by Covestro Coating Resins BV.
2) Additional data. August 2023. Submitted by Covestro Coating Resins BV.

References

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2021. Note for Guidance for the preparation of an application for the safety assessment of a substance to be used in plastic Food Contact Materials (update 2021). EFSA Journal 2008, 6(7):21r, 41 pp. https://doi.org/10.2903/j.efsa.2008.21r

EFSA Scientific Committee, 2011. Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379, 69 pp. https://doi.org/10.2903/j.efsa.2011.2379

European Commission, 2001. Guidelines of the Scientific Committee on Food for the presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out82_en.pdf

Abbreviations

AChE	acetylcholinesterase
CAS	chemical abstracts service
EFSA	European Food Safety Authority
FCM	food contact materials
IC50	the concentration of a drug or inhibitor needed to inhibit a biological process or response by 50%
OECD	Organisation for Economic Co-operation and Development
Kow	n-octanol/water partition coefficient
QSAR	quantitative structure-activity relationship
TTC	Threshold of Toxicological Concern
SCF	Scientific Committee on Food
SML	specific migration limit
TG	test guideline