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Derivation of the indicative Drinking Water Target Value for TRC233

TECHNICAL REPORT

Report for

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Executive Summary

Wood was retained by Sitech IAZI bv to derive a substance specific indicative drinking water target value for the TRC233 polymer (CAS# 40623-75-4 and CAS# 77019-71-7 for the corresponding sodium salt) using the formal RIVM guidance. The TRC233 polymer is an important ingredient in conditioning agents used to protect the proper functioning of industrial cooling systems.

As there is no information available regarding to adverse effects of the TRC233 polymer to mammals, the drinking water target value is derived from the toxicological data related to the constituents. Based on the properties of the constituents of the TRC233 polymer, the proposed value for the drinking water target value is conservatively set at 4,4 mg/L.

Sitech IAZI bv requests the Wetenschappelijke Klankbordgroep normen water en lucht to evaluate and approve the proposed value for the indicative drinking water target value for the TRC233 polymer and its sodium salts as well as the derived values for the constituents as summarized in below table.

Proposed indicative drinking water target values

Substance	Proposed DTV in mg/L
Poly acrylic acid (AA (CAS# 9003-04-7))	4,4
2-acrylamido-2-methylpropyl sulfonic acid (AMSA)	11
Poly 2-acrylamido-2-methylpropyl sulfonic acid (pAMSA)	11
HAPNQ (CAS# 276878-97-8)	5,5
TRC233 (CAS# 40623-75-4)	4,4
Sodium salt of TRC233 (CAS# 77019-71-7)	4,4

Please note that in this report a comma is used as decimal separator as defined in the methodology to derive (indicative) environmental quality standards [RIVM, 2015]. A point is used as a thousand separator as appropriate.

Contents

1. Introduction

Sitech IAZI bv, hereafter Sitech, operates a wastewater treatment plant at the Industrial Park Chemelot, hereafter referred to as IAZI. The IAZI receives and treats most of the wastewater generated at the site, including the purges from cooling water systems. Before mentioned purges contain cooling water conditioning chemicals, like biocides, dispersants and anti-fouling agents.

Present wastewater discharge permit holds an obligation to minimize the use of the dispersants ATMP (CAS# 6419-19-8) in order to prevent the generation of AMPA (CAS# 74341-63-2) in the IAZI due to biodegradation of ATMP. As AMPA is a persistent chemical, one of the adverse effects of the discharge with the effluent is potential exceedance of the limit value for the intake of surface water for the preparation of drinking water.

Over the past years, Sitech has investigated potential alternatives to replace ATMP as a cooling water dispersant. Products comprising the so-called TRC233 polymer (CAS# 40623-75-4, CAS# 77019-71-7 for the corresponding sodium salt) are listed as potential alternatives for ATMP.

The potential impact of the discharge of TRC233 with the effluent of the IAZI on the functions of the receiving water body, like any other discharge of chemical contaminants, needs to be assessed according to the so-called immissietoets (discharge test). In the underlying situation the potential adverse effects of the discharge in regard to aquatic ecology and the drinking water preparation functions are relevant. Below table presents the criteria which are used in the discharge test supporting the application for a new discharge permit.

Table 1.1 Overview of relevant impact assessment parameters for TRC233

Function of receiving water body	Distance to discharge point (km)	Dilution factor of the discharge (-)	Water quality parameter	
			Parameter	Value (µg/L)
Ecology	0,6	4,13	JG-MKE	180
Intake of surface water for the preparation of drinking water	± 20	22,1	Signal value	1

From table 1.1. it can be derived that the function "surface water for the preparation of drinking water" is the most restrictive. This is mainly due to the application of the generic, non-substance specific, signal value.

Because the properties of the TRC233 polymer, like low bioavailability due to the size of the molecule, it can be anticipated that a substance specific drinking water parameter will have a significant higher value.

The Dutch National Institute for Public health and the Environment compiled a formal guidance on the derivation of substance specific drinking water parameters [RIVM, 2017] which aligns with the procedures of the European Commission. The European Commission published an update of the Guidance Document in 2018 [EC, 2018].

Wood was asked by Sitech to derive a substance specific drinking water parameter for TRC233 using the formal guidance documents. This report describes results of literature research and suggests a value for a specific drinking water parameter for the TRC233 polymer.

Please note that in this report a comma is used as decimal separator as defined in the methodology to derive (indicative) environmental quality standards [RIVM, 2015]. A point is used as a thousand separator as appropriate.

2. Generic approach to derive a drinking water target value

The procedure to calculate a substance specific drinking water target is described in RIVM report 2017-0091 [RIVM, 2017] in concordance with Guidance Document No. 27 [EC, 2018]. The drinking water target value is calculated from the Derived No Effect Level Tolerable, DNEL, or the Tolerable Daily Intake (TDI) using below formula:

$$DTV = \frac{BW * DNEL * \max\_fraction}{DI}$$

with

DTV =	drinking water target value (mg/L)
BW =	average body weight (= 70 kg)
DNEL =	Derived No Effect Level, like the Tolerable Daily Intake in mg per kg body weight per day or the Acceptable Daily Intake in mg per kg body weight per day
max_fraction =	Maximum uptake as a percentage of the DNEL (20%)
DI =	Average daily water consumption (= 2 L / day)

Resulting in

$$DTV = \frac{70 * DNEL * 20\%}{2} = 7 * DNEL$$

Appendix E presents flow diagrams to derive drinking water target values as set by RIVM guidance [RIVM, 2017].

3. Stepped derivation of the drinking water target value for TRC233

The TRC233 polymer is used as a water treatment agent to control the fouling of amongst other, industrial cooling systems. Products comprising the TRC233 polymer can be suitable to replace agents based on organic phosphates which are traditionally used for this purpose.

The TRC233 polymer is predominantly a copolymer of two organic acids with small amounts of a monomer with luminescent properties. Latter monomer supports the optimal dosage of the TRC233 polymer to the cooling water system.

According to US patent 5,284,590 the TRC233 polymer is a water-soluble polymer comprising

- Acrylic acid (AA)
- 2-acrylamido-2-methylpropyl sulfonic acid (AMSA)

The molecular weight ranges from about 1.000 to 12.000. The weight ratios of the AA versus AMSA vary from 4 : 1 to 1 : 1. The preferred weight ratio for the TRC233 polymer as mentioned in the patent is 1,5 : 1. In order to support optimal dosage of the TRC233 containing product to cooling water systems, as small amount of a fluorescent monomer is integrated in the polymer. In the underlying case, HAPNQ (CAS# 276878-97-8, 4-methoxy-N-(3-N,N-dimethylaminopropyl)naphta) is incorporated in the polymer.

To derive a drinking water target value, a literature search was executed regarding the TRC233 polymer using CAS# 77019-71-7. This specific TRC233 polymer is an active component of a cooling water chemical which is used at the Industrial Site Chemelot at Geleen, the Netherlands. Appendix A presents available base information for this polymer.

As the literature search did not result in any relevant toxicological information, the drinking water target value is to be derived using an alternative methodology. The generic fallback scenario is to use the so-called Cramer classification as starting point for the drinking water target value. The scenario is not appropriate in the case of polymers. Consequently, the drinking water target value for the TRC233 polymer is to be derived based on a read-across of comparable polymers. As the TRC233 basically is a carboxylic acid polymer, the constituents polyacrylate (pAA) and poly-(2-Acrylamido-2-Methyl-1-Propane-Sulfonic acid (pAMSA) are used for this purpose.

Appendix B and Appendix C present the results of a literature search for pAA and pAMSA respectively. In Appendix D the result of a literature search for HAPNQ is presented. For all constituents of the TRC233 polymer, a specific drinking water target value is derived. A summary of the relevant properties of both polymers is presented in table 3.1.

Table 3.1 Summary of relevant toxicological data for pAA, pAMSA and HAPNQ

Parameter	pAA	pAMSA (AMSA)	HAPNQ
LD50 oral Rat	>5.000 mg/kg-bw	16.000 mg/kg-bw	> 2.000 mg/kg-bw
Skin irritation	Not irritant under test conditions	Not irritant under test conditions	Not irritant under test conditions
Eye irritation		Not irritant under test conditions	Not irritant under test conditions
Skin sensitization		No conclusive evidence under test conditions	

Table 3.1 Summary of relevant toxicological data for pAA, pAMSA and HAPNQ (continued)

Parameter	pAA	pAMSA (AMSA)	HAPNQ
Repeated dose toxicity oral (NOAEL)	1.136 mg/kg-bw/day	1.000 mg/kg-bw/day	473 mg/kg-bw/day
Genetic toxicity (in vitro)	No mutagenic activity observed	No significant increase of revertants	No mutagenic activity observed
Genetic toxicity (in vivo)	No increase in micronucleus induction observed	Non-clastogenic under test conditions	
Reproductive toxicity (NOEL)	375 mg/kg-bw/day	1.000 mg/kg-bw/day	

Based on the data in table 3.1 the DNEL for pAA, pAMSA and HAPNQ are derived from the NOAEL for repeated dose toxicity oral. The results are presented in table 3.2.

Table 3.2 Derivation of the DNEL for pAA, pAMSA and HAPNQ

Parameter	pAA	pAMSA (AMSA)	HAPNQ
NOAEL	375 mg/kg-bw/day	1.000 mg/kg-bw/day	473 mg/kg-bw/
Assessment factors			
Subacute to chronic duration	6	6	6
Rat to human	10	10	10
Intraspecies variability	10	10	10
DNEL	0,625 mg/kg-bw/day	1,67 mg/kg-bw/day	0,78 mg/kg-bw/day

The indicative drinking water target value is derived from the calculated DNEL using below formula. The derived values are presented in table 3.3.

$$DTV = \frac{BW * DNEL * \max\_fraction}{DI} = 7 * DNEL$$

Table 3.3 Derivation of the indicative drinking water target value for pAA, pAMSA and HAPNQ

Parameter	pAA	pAMSA (AMSA)	HAPNQ
DNEL	0,625 mg/kg-bw/day	1,67 mg/kg-bw/day	0,78 mg/kg-bw/day
DTV	4,38 mg/L	10,9 mg/L	5,52 mg/L

Above derivation of the indicative drinking water target values for the constituents of the TRC233 polymer is executed. Using the result as a read-across assessment of the adverse effects of the TRC233 polymer

itself, the value for the indicative drinking water target value is conservatively based on pAA. Hence the value for the indicative drinking water target value is set at 4,4 mg/L (rounded to two digits).

4. Discussion

As stated above, the TRC233 polymer consists of AA and AMSA in weight ratios varying from 4 : 1 to 1 : 1 with a typical ratio of 1,5 : 1. The TRC233 polymer also comprises 2% HAPNQ.

Given these ratios and the derived indicative drinking water target values for pAA, pAMSA and HAPNQ, the value for the indicative drinking water target value for the TRC233 polymer varies between the values presented in table 4.1.

Table 4.1 Influence of the monomer weight ratio on the DTV value for the TRC233 polymer with 2% HAPNQ

98% pAA and or pAMSA		2 % HAPNQ	DTV for TRC233 (in mg/L)
Fraction of AA	Fraction of AMSA	Fraction HAPNQ	
0,0	1,0	1	11
0,5	0,5	1	7,6
0,6	0,4	1	7,0
0,8	0,2	1	5,7
1,0	0,0	1	4,4

Based on the data in table 4.1, the indicative drinking water target value for the TRC233 polymer varies between 4,4 mg/L and 11 mg/L. The TRC233 polymer typically contains more AA monomers than AMSA monomers. Given the typical ratio of 1,5 : 1 (AA : AMPS), this would suggest a value of 7,0 mg/L for the TRC233 polymer (rounded to two digits). This value for the iDTV for TRC233 is significantly higher than the proposed value of 4,4 mg/L as derived based on the read across in chapter 3. Hence the proposed value of 4,4 mg/L can be classified ad a conservative value.

In order to monitor the ultimate discharge of the TRC233 to surface water, Sitech IAZI BV together with the supplier of the polymer, is developing an improved protocol for the analysis of the TRC233 polymer in the effluent of the waste water treatment plant. The detection limit of the present analysis protocol, which is based on the fluorescent properties of HAPNQ in the polymer, is 0,2 mg/L. Hence, present analysis protocol is adequate to monitor TRC233 levels in surface water to safeguard safe water extraction for the preparation of drinking water.

The main functionality of the TRC233 polymer is to bind and disperse bivalent cations, like Calcium and Magnesium, in order to prevent scaling in industrial cooling water systems. These properties result in a high removal in a wastewater treatment plant, predominantly because of adsorption to sludge.

Discharged amounts of the polymer will behave in a similar manner in surface water and the water treatment facilities drinking water companies apply in the production of drinking water. Treatment systems used for the production of drinking water from surface water typically comprise sand filtration and activated carbon adsorption. This implies that TRC233 polymer present in surface water used for the preparation of drinking water will be removed with a high efficiency as well thus further reducing potential risk for public health.

5. Proposed substance specific indicative drinking water target values

Below table presents an overview of the proposed indicative drinking water target values.

Table 5.1 Proposed indicative drinking water target values

Substance	DTV in mg/L
Poly acrylic acid (AA (CAS# 9003-04-7))	4,4
2-acrylamido-2-methylpropyl sulfonic acid (AMSA)	11
Poly 2-acrylamido-2-methylpropyl sulfonic acid (pAMSA)	11
HAPNQ (CAS# 276878-97-8)	5,5
TRC233 (CAS# 40623-75-4)	4,4
Sodium salt of TRC233 (CAS# 77019-71-7)	4,4

6. References

EC, 2018. "Technical Guidance for Deriving Environmental Quality Standards"; Guidance Document No. 27, updated version 2018.

Min IenW, 2019. "Handboek immissietoets, versie 2019"; Ministerie van Infrastructuur en Milieu, Rijkswaterstaat; concept document versie oktober 2019.

RIVM, 2015. "Handleiding voor de afleiding van indicatieve milieurisicogrenzen"; RIVM Rapport 2015-0057, L.R.M. de Poorter et al, RIVM Centrum voor Veiligheid van Stoffen en Producten.

RIVM, 2017. "Evaluatie signaleringsparameter nieuwe stoffen drinkwaterbeleid"; RIVM Rapport 2017-0091, N.G.F.M. van der Aa et al, RIVM Centrum voor Veiligheid van Stoffen en Producten.

Appendix A
Base information TRC233 polymer

Identification and classification

Name	TRC233
IUPAC-name	TRC233
Synonyms	TRC233
CAS-number	40623-75-4 77019-71-7 for the corresponding sodium salt
Chemical group according to EPIwin	Polymers
Cramer class	Not applicable
Know uses	Dispersant to control fouling in industrial cooling water systems
Toxicity mechanism	-
Harmonized classification	TBD
Molecule formula	Not applicable. The typical polymer consists of acrylic acid and 2-acrylamido-2-methylpropyl sulfonic acid in a weight ratio of 1,5 : 1 in combination with <1% 4-methoxy-N-(3-N,N-dimethylamino-propyl)-naphta
Smiles	-
Molecule structure	-

Fysico-chemical properties and dispersion

Property	Value	Additional information	Reference
Molecular weight (g/mol)	6.000 – 12.000		US patent 5,284,590
Melting point (°C)	No data		
Boiling point (°C)	No data		
Vapour pressure (Pa)	No data		
Solubility in water (mg/L)	Complete		
Log K_{ow}	<0		Expert judgement
Henry-coëfficiënt (Pa m^3/mol)	No data		
pKa	No data		

Appendix B
Derivation of the indicative drinking water target value for Polyacrylic acid (pAA)

Summary

The HERA report on polyacrylic acid (PAA) has been used as the basic document for toxicity information. The lowest NOAEL was selected from a range of toxicological endpoints in studies with rodents. The lowest NOAEL was found to be 375 mg/kg-bw/day related to the reproductive and developmental toxicity in rats. This NOAEL was taken as starting point for deriving a maximum concentration in drinking water. For deriving a DNEL (Derived No Effect Level) of PAA for the general population, the following assessment factors were considered:

- subacute to chronic duration (6)
- interspecies variability (10)
- intraspecies variability (10)

Applying above assessment factors to the lowest NOAEL results into a DNEL for the general population of (375/(6*10*10) =) 0,625 mg/kg-bw/day. In addition, the daily dose via drinking water uptake (2 litres at 70 kg bodyweight per day) may not exceed 20% of the DNEL of the general population.
This results in a drinking water limit of (20%*70*0,625/2 =) 4,4 mg PAA per litre (rounded to two digits).

1. Introduction

Poly-acrylic acid belongs to the category of polycarboxylate polymers. Polycarboxylate polymers were developed to replace the functions of phosphates in cleaning products, which were phased out due to environmental concerns regarding eutrophication. They enhance the efficiency of surfactants by preventing precipitation of calcium salts due to interaction of Ca^{2+}-ions with the carboxylic acid groups. They are constituents of automatic dishwashing detergent and laundry detergent booster-machine cleaning agents. The typical molecular weight is about 4500 (about 62 times the backbone acrylic acid, figure 1).

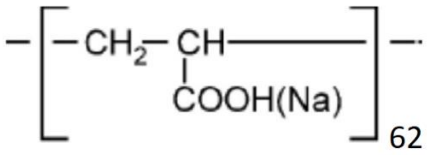

Fig 1: Back bone polyacrylic acid

If the carboxylic groups are occupied by an H^+-ion, the aqueous solution has a low pH and is irritant to the eyes and the skin. If all carboxylic groups contain a Na^+-ion, the pH is about neutral. This is shown in figure 2 for a polymer consisting of 14 acrylic acid backbones.

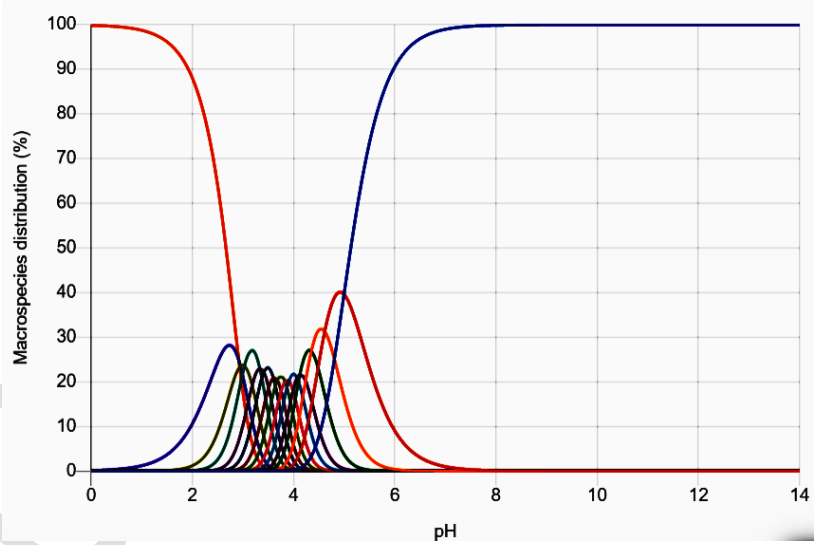

Fig. 2 (ChemAxon estimation model)

In this note the focus is on the sodium salt of polyacrylic acid. The solubility of this salt in water is very high, but in a wastewater treatment plant a lot is adsorbed to the activated sludge. The typical partition ratio (Kd) between activated sludge and water is about 1825 litres/kg and is dependent on the calcium content of the sludge. If the sludge contains a lot of calcium salts the Kd may be up to one order of magnitude higher.

Nevertheless, the sodium salt of polyacrylic acid is discharged via the effluent of the wastewater treatment plant to surface water. The toxicity for aquatic and benthic organisms is so limited, that it is far above the limit concentrations, which hazard labelling for the environment makes obligatory (DeLeo et al 2020).

River water is also the raw material for drinking water. The technical processes for the preparation of drinking water are not always able to remove completely the polyacrylic acid sodium salt from the drinking water. This note reviews the existing toxicological information of the sodium salt of polyacrylic acid with the aim to derive a limit for the sodium salt of polyacrylic acid in drinking water.

2. Toxicological information on the sodium salt of polyacrylic acid (PAA-Na, CAS 9003-04-7)

The toxicology of PAA-Na has been studied and reported by the HERA (Human and Environmental Risk Assessment) project participants, a European voluntary initiative launched in 1999 by the following organisations:

- A.I.S.E. representing the formulators and manufacturers of household and maintenance cleaning products.
- CEFIC representing the suppliers and manufacturers of the raw materials.

HERA has issued the 3rd version of the report on the Human and Environmental Risk Assessment in 2014. This report is to be downloaded from https://www.heraproject.com/files/HERA_P-AA_final_v3_23012014.pdf

The report shows that PAA-Na has such a low toxicity, that there is no obligation to classify this substance as a hazardous substance according to the REACH-CLP requirements (CLP= Classification, Labelling and Packaging).

The toxicological findings form the HERA report have been summarized in the following paragraphs:

2.1 Acute oral toxicity (rat)

The acute oral toxicity was studied in rats for PAA-Na with different average molecular weight (1.000 through 7.800). The LD50 appeared to be larger than 5 grams per kg bodyweight.

2.2 Acute dermal toxicity(rabbit)

The acute dermal toxicity was studied in rabbits for PAA-Na with different average molecular weights (1.000 – 4.500). The acute dermal LD50 was found to be larger than 5 grams per kg bodyweight.

2.3 Acute inhalation toxicity (LC50 4 hours)

No references found to this type of study.

2.4 Skin Irritation

Several skin irritation studies on rabbits were done with P-AA of different molecular weights (1.000-78.000), in concentrations between 15-45% or neat undiluted material. Exposure was for 4 h -24 h with occlusive or semi-occlusive dressing. All studies show no skin irritation potential.

2.5 Skin sensitisation

PAA-Na with an average molecular weight of 4.500 or 78.000 were tested for skin sensitisation in the guinea pig maximisation test (GMPT). The test concentrations in contact with the skin were between 5 and 20%. PAA-Na showed no sensitising potential in the GMPT as a low or high molecular weight polymer.

2.6 Repeated dose toxicity (oral)

Polyacrylic acid (average molecular weight 2.500, neutralized with sodium hydroxide) has been tested in a Non-Guideline study with substance application via oral feed for 28 days to examine the effect of the test substance on mineral homeostasis.
Six male rats were fed 2,5% of the test substance in the diet (about 1.136 mg/kg-bw/day). Growth, weight and appearance of the animals were normal throughout the study. In the last week, a small but significant decrease in the total weight of bone minerals was detected and confirmed by radiographic and histological examination. The concentration of magnesium in the bones and the plasma of the treated animals were significantly decreased. Calcium loss was slight and not statistically significant. Urinary excretion of sodium and phosphorus was markedly increased. Excretion of calcium was slightly increased. The result was interpreted by the authors to be due to a metabolic or nutritional imbalance rather than to a systemic toxicity. The excretion of sodium might have been increased by the high uptake of the sodium-neutralized test substance. The applied dose was therefore interpreted as a NOAEL (No Observed Adverse Effect Level).

2.7 Repeated dose toxicity by inhalation

The maximum dose level in rodent inhalation studies (maximum 5 mg/m3) for 6 hours per day (inhalation volume of 0,3 m3/kg-bw/day) result into a daily systemic exposure of 1,5 mg/kg-bw/day and is much lower than in the oral study. Inhalation studies on PAA are irrelevant for deriving a DNEL via ingestion.

2.8 Repeated dose toxicity by dermal exposure (bath water)

The molecular weight of PAA of from 1.000 through 70.000 is too high to permeate through the stratum corneum of the human skin. Repeated dose toxicity studies via dermal exposure are not available.

2.9 Genetic toxicity in vitro

PAA (molecular weight 100-4.500) were tested for mutagenic activity in vitro in the Ames test, mouse lymphoma assay, chromosome aberration assay, unscheduled DNA assay etc. These tests are able to detect point and frameshift mutations and chromosome breaks. No mutagenic activity was observed in these in vitro tests.

2.10 Genetic toxicity in vivo

PAA (molecular weight 2.000) has been tested in a mouse micronucleus assay using groups of 5 male and 5 female mice. The test substance or sterile distilled water (control vehicle) was administered by gavage at a volume of 20 ml/kg. Animals were dosed by gavage with the maximum tolerated dose (13.850 mg/kg bw) and observed over a 3-day period. Positive control animals were i.p. injected with mitomycin C that was prepared in sterile 0,9% saline at a concentration of 0,2 mg/ml. Animals were killed at 24, 48 and 72 h after dosing, bone marrow cells were harvested and 1.000 cells per animal were examined for micronuclei in polychromatic erythrocytes and also for the ratio for polychromatic to normochromatic erythrocytes.
During the experiment 3 female mice died, 1 at each of the harvest times. Clinical signs of piloerection, hunched posture and lethargy were observed following dosing. No increase in micronucleus induction was observed in the groups administered the test substance at any of the harvest times, when compared with the controls.

2.11 Carcinogenicity

Carcinogenicity studies have not been performed for PAA. Carcinogenicity studies are not considered to be relevant considering the chemical structure and the absence of any mutagenic activity in experimental studies in vitro and in vivo.

2.12 Reproductive and developmental toxicity

Test results

Developmental toxicity (teratogenicity) of PAA has been studied in rats for an average molecular weight of 4.500 and 90.000. The doses were applied by gavage during the period of organogenesis (8 – 10 days). PAA (MW 4.500) was applied at dose levels of 0, 500, 1.000, and 3.000 mg/kg-bw/day and PAA (MW 90.000) at dose levels of 0, 125, 375 and 1.125 mg/kg-bw/day.

Seven dams died during the last study (PAA-MW 90.000), of which 4 mortalities were caused by mal-intubation. However, the authors of the latter study attributed 3 mortalities at the highest dose group to treatment with PAA (MW 90.000). This is probably not a correct interpretation of the test results as PAA (MW 90.000) is at least 10 times less absorbed from the intestines due to the 20 times higher molecular weight (90.000 versus 4.500, see Loehry et al. 1970).

The highest dose level of PAA (MW 4.500) was applied at 3.000 mg/kg-bw/day, while PAA (MW 90.000) was given at a dose of 1.125 mg/kg-bw/day. Despite the fact that there was not any effect observed at the highest dose level of 1.125 mg/kg-bw/day on the body weight of the dams and pups and body weight gain of the dams compared to the control group, the NOAEL for PAA 90.000 is set at 375 mg/kg-bw/day..

The NOAEL for PAA (MW 4.500) appeared to be 3.000 mg/kg-bw/day related to maternal and to developmental toxicity.

3. Derivation of a drinking water limit for the sodium salt of polyacrylic acid

In the 28-day repeated dose study in rats the highest dose without any effect appeared to be 375 mg/kg-bw/day, based on the repeated dose oral toxicity.

In the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2.1 November 2012) has been stated how such an acute NOAEL should be translated to a Derived No Effective Level for consumers via extrapolation assessment factors:

rat to human	10
general population	10
28 days to 2 year rat	6

This results into a DNEL of 375 / (10*10*6) = 0,625 mg/kg-bw/day for humans.

There is an additional limitation in the Netherlands for drinking water. Drinking water may not contribute more than 20% of the total DNEL to the daily body burden in a daily drinking water volume of 2 litres at a body weight of 70 kg. This means that the total mass of PAA in drinking water may not exceed 20%*70*0,625/2 = 4,38 mg/litre.

4. References

DeLeo PC, Summers H, Stanton K, Lam MW, 2020. Environmental risk assessment of polycarboxylate polymers used in cleaning products in the United States. Chemosphere. 258:127242.

HERA, 2014. Polyacrylic acid homopolymers and their sodium salts (CAS 9003-04-7) https://www.heraproject.com/files/HERA_P-AA_final_v3_23012014.pdf

Loehry CA, Axon AT, Hilton PJ, Hider RC, Creamer B, 1970. Permeability of the small intestine to substances of different molecular weight. Gut. 11(6):466-70.

Appendix C
Derivation of the indicative drinking water target value for polyacrylaminomethylpropanesulphonic acid (pAMPS)

Summary

Poly-AMPS, or poly-(2-Acrylamido-2-Methyl-1-Propane-Sulfonic acid), is an organic polymer. It has been detected in river water, which is used as raw material for drinking water. Studies on the toxicity of poly-AMPS have not been published. Toxicity data on the monomer, AMPS, are available as part of the chemical registration in the scope of the European REACH legislation.

The NOAEL (No Observed Adverse Effect Level) of mono-AMPS.NH_4 was found to be 1.000 mg/kg-bw/day in Sprague Dawley rats, dosed by gavage in 5 ml water per kg-bw per day. The duration of the study was 28 days. A human lifetime DNEL (Derived No Effect Level) was estimated from this NOAEL accounting for duration, interspecies and intraspecies variability using the following assessment factors:

- Subacute to Chronic Duration 6
- Interspecies 10
- Intraspecies 10

Applying above assessment factors to the lowest NOAEL results into a DNEL of 1,67 mg/kg-bw/day for the general population regarding AMPS.NH_4. In addition, the daily dose via drinking water uptake (2 litre at 70 kg bodyweight per day) may not exceed 20% of the DNEL of the general population. This means that the total mass of AMPS as ammonium salt in drinking water may not exceed 20%*70*1,67/2 = 11,7 mg AMPS.NH_4 per litre or 10,9 mg AMPS as the acid.
The drinking water standard for mono-AMPS is set to 11 mg/litre (rounded to two digits).

The systemic toxicity of mono- and poly-AMPS is assumed to be similar because both chemicals are highly soluble in water and both share the same chemical groups.

Mono-AMPS is assumed to be fully absorbed in the small intestines. The intestinal absorption is decreasing with increasing molecular weight of poly-AMPS. The systemic availability of poly-AMPS decreases with increasing molecular weight. In this way the drinking water standard of mono-AMPS may be applied to poly-AMPS as a conservative assessment.
The drinking water standard for poly-AMPS is set to 11 mg/litre, the same value as for mono-AMPS.

1. Introduction

Poly-AMPS, or poly(2-Acrylamido-2-Methyl-1-Propane-Sulfonic acid) is an organic polymer. It is water-soluble, forms hydrogels and is used as a strong anionic polyelectrolyte. It is used as flocculant for water treatment. In the hydrated state, the AMPS homo- and copolymers exhibit high proton conductivity. They form excellent materials for proton conducting membranes in Direct Methanol Fuel Cells, used for generating electric power.

Poly-AMPS has been detected in river water, which is used as raw material for drinking water. This material is not readily biodegradable and is not removed in the process of preparing drinking water from river water.

There is a need to collect information on the mammalian toxicity of poly-AMPS in order to derive a indicative limit for poly-AMPS in drinking water.

1.1 Molecular structure of the monomer AMPS and decamer of AMPS

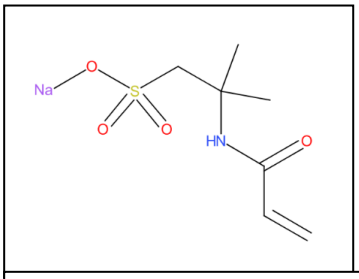

Figure 1:
Monomer, AMPS (2-Acrylamido-2-Methyl-1-Propane-Sulfonic acid) sodium salt (CAS #5165-97-9)

Monomer, AMPS (free acid CAS #15214-89-8)

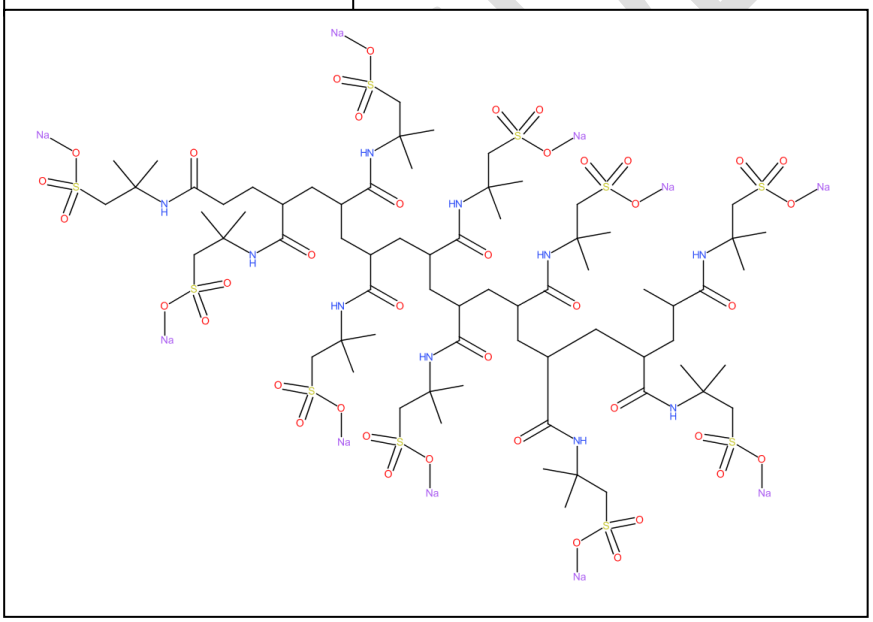

Figure 2:
Polymer of 10 repeating units of AMPS as sodium salt (CAS #35641-59-9)
The salt is not listed in the ECHA CLP regulation.

Poly-AMPS, free acid
(CAS #27119-07-9)
The free acid is listed as a corrosive substance for the skin in the ECHA CLP regulation (ECHA 2020a)

1.2 Physicochemical properties and structure

According to the classification provided by companies to ECHA in **CLP notifications,** poly-AMPS polymer (CAS #27119-07-9) causes severe skin burns and eye damage and causes serious eye irritation (ECHA 2020a). The sulfonic acid groups in poly-AMPS react in water as a strong acid.

At a pH>3 all sulfonic acid groups have lost its H^+-ion. The pH of the environment is between 7,5 and 8. This means that in the environment poly-AMPS exists mainly as sodium, calcium, magnesium or ammonium salt. It becomes then a neutral water-soluble sulfonic acid salt comparable with sodium sulphate, but with a higher molecular weight (EPA 2019). The molecular structure does point to a chemically inert molecule. Based on the structure it is to be expected, that the salt of AMPS is not a skin sensitizer, is hardly toxic, is not mutagenic nor carcinogenic nor reprotoxic nor endocrine modulating etc.

2. Experimental toxicological findings.

Toxicological data on the sodium salt of poly-AMPS from standard toxicology testing have not been published. A limited data set has been presented for the neutral salt of the monomer in the ECHA registration file. The tests were carried out following widely adopted OECD testing guidelines under GLP conditions. The results are summarised below.

2.1 LD50 oral rat

The sodium salt of AMPS was dosed to rats up to 16.000 mg/kg-bw following OECD guideline 801. Mortality did not occur. The substance may be considered as practically non-toxic.

2.2 Skin irritation

The sodium salt of AMPS was studied for skin irritation according to Guideline EPA OPPTS 870.2500. Very slight erythema was observed on the dose site of 3 of 6 animals at 1 hour following the end of the contact period; it subsided within 24 hours. The substance appeared to be not a skin irritant under the test conditions.

2.3 Eye irritation

The sodium salt of AMPS was studied for eye irritation according to Guideline EPA OPPTS 870.2400. Moderate conjunctival irritation was apparent in the dosed eyes of all 6 rabbits. All rabbits had a normal ocular appearance within 72 hours to 4 days. The test substance was considered to be not irritating to eyes under the test conditions.

2.4 Skin sensitisation

The ammonium salt of AMPS was studied for skin sensitisation in the guinea pig maximisation test according to the European protocol B6. Under the conditions of this study, the test substance did not produce evidence of skin sensitisation (delayed contact hypersensitivity) in nine of the ten test animals. The remaining animal gave an inconclusive response.

2.5 Repeated dose toxicity

The repeated dose toxicity over 28 days was studied with the ammonium salt of AMPS, following the OECD testing guideline 407 under GLP. Groups of 10 male and 10 female rats received doses of 5 ml/kg-bw/day by

gavage, resulting in daily dose levels of 0, 50, 150, 400 and 1.000 mg/kg-bw. Clinical signs, mortality, body weight, body weight gain, blood chemistry, haematology, urinalysis, organ weights, macroscopic and microscopic pathology of 29 organs were not statistically different between the highest dose and the control group. The NOAEL (No Observed Adverse Effect Level) via gavage was stated to be 1.000 mg/kg-bw/day.

2.6 Genetic toxicity in vitro

AMPS as acid was tested in the Ames test (bacterial reverse mutation assay with several strains of Salmonella typhimurium and Escherichia Coli) following OECD Guideline 471 and 472 under GLP conditions. The test substance was slightly toxic to all Salmonella strains at the highest dose used (5.000 microgram/plate) both with and without metabolic activation. For all bacterial strains tested there was no significant increase in the number of revertants at any dose of test material when compared to the corresponding negative solvent control. The entire assay was repeated, and the results seen in the first experiment were confirmed. The positive and control solvent control for all experiments were within established historical ranges for each bacterial strain utilized. AMPS did not produce a significant increase in the number of revertants, with and without metabolic activation in any test strain.

2.7 Genetic Toxicity in vivo

AMPS in the acid form was studied for chromosome aberration in the bone marrow of the rat following the OECD guideline 475 under GLP conditions. Five Sprague Dawley rats per sex per dose were dosed by gavage. The single dose levels were 0, 50, 150 and 1.500 mg/kg-bw. The animals were euthanised 6, 18 and 24 hours. The bone marrow was taken from the femurs or tibias and further processed for microscopic analysis.
Mean body weights of the dose groups were not significantly different from the vehicle control group at any time point. The test substance did not produce statistically significant increases ($p<0,05$) in the percentage of cells with aberrations at any dose, time period or for either sex, compared to control values. Positive control animals treated with cyclophosphamide (30 mg/kg) demonstrated an increase in the frequency of damaged cells which was statistically significant at the study threshold of $p<0.05$. Thus, the positive and negative controls demonstrated the reliability of the assay to detect chromosomal aberrations. AMPS was non-clastogenic in rat bone marrow cells under the conditions of the assay.

2.8 Reproductive toxicity

The ammonium salt of AMPS was studied for reproductive toxicity in the reproduction / developmental toxicity screening test following the OECD guideline 421 under GLP conditions. A number of 12 Sprague Dawley rats per sex per dose were exposed via gavage to a daily dose of 0, 100, 500 or 1.000 mg/kg-bw.
Oral administration had no effect on F0 survival, growth, mating behaviour, copulation, fertility, precoital intervals, gestation lengths, corpora lutea counts, implantation counts, mean live litter size, prelpost-implantation loss, gross necropsy findings or organ weights (testes and epididymides). Histopathological examination of the testes, ovaries and epididymides from control and high-dose rats did not reveal any test article-related microscopic changes. No test article-related effects were observed in the F1 offspring with respect to survival, clinical observations, body weights or gross necropsy findings. In addition, there were no indications of test article-related developmental effects in the F1 pups at any dosage level tested. Based on the results, a dosage level of 1.000 mg/kg/day was considered a no-observed-effect level (NOEL) for this reproduction and developmental screening study in rats.

Conclusions on toxicological findings

AMPS as salt is not irritant for the skin and eyes. It is not mutagenic in vitro and in vivo. This means, that there is no need for a carcinogenicity study.
The acute toxicity is very low with an oral LD50 rat of > 16.000 mg/kg. This is less toxic than table salt.
Reproductive toxicity was not observed at the highest dose level of 1.000 mg/kg-bw/day (poly-AMPS ammonium salt) in the Sprague Dawley rat.
The NOAEL (No Observed Adverse Effect Level) in a 28-day repeated dose toxicity study was found to be 1.000 mg/kg-bw/day of the poly-AMPS ammonium salt.

3. Derivation of a safe level of AMPS in river water as raw material for drinking water.

The point of departure is the NOAEL in a 28-day repeated oral dose toxicity study in the Sprague Dawley rat. This NOAEL (1.000 mg/kg-bw/day) was taken as starting point for deriving a maximum concentration in drinking water. For deriving a DNEL (Derived No Effect Level) for the general population, an assessment factor of 600 was used considering:

- subacute to chronic duration (6)
- interspecies variability (10)
- intraspecies variability (10)

This results into a DNEL of (1.000 / (6*10*10 =) 1,67 mg AMPS.NH4 per kg-bw per day.

There is an additional limitation in the Netherlands for drinking water. Drinking water may not contribute more than 20% of the total DNEL to the daily body burden in a daily drinking water volume of 2 litre at a body weight of 70 kg. This means that the total mass of AMPS as ammonium salt in drinking water may not exceed 20%*70*1.67/2 = 11,7 mg AMPS.NH_4 per litre or 10,9 mg AMPS per litre as the acid.

4. Extrapolation of toxicity from the monomer of AMPS to poly-AMPS

AMPS as sodium salt is a very water-soluble substance with a molecular weight of 229.23 and an ionized sulfonic acid group. The estimated log(Kow) of AMPS.Na is -4,34 (EPA 2019). This means that the water solubility is of AMPS high. AMPS.NH_4 was dissolved in water up to 20 % (1000 mg in 5 ml water) as dosing solution by gavage in the repeated dose toxicity study for 28 days. This points to a high water-solubility of mono-AMPS.NH_4.

It is expected that the poly-AMPS is also very water soluble. The log(D) is the equivalent of log(Kow) for ionizable substances. The log(D) of poly-AMPS (10 backbone units) has been estimated to be – 26,9 (Chemicalize 2020). This points to a very high water-solubility and explains the gel formation at high concentrations of poly-AMPS in water.

Because of the high water solubility of the mono en poly-AMPS and because of the similarity of chemical groups of the backbone units it is assumed, that the systemic toxicity of both the monomer and the polymer of AMPS.Na will be in the same order of magnitude.

Amino-ethane-sulfonic acid (taurine) is fast absorbed form the intestinal tract (Nielsen et al. 2017). Mono-AMPS has some structural features of taurine like an amide and a sulfonic acid group. Therefore, it is assumed that mono-AMPS as a salt will be fast absorbed from the intestinal tract in the blood and subsequently excreted

via the kidneys. It is to be expected that the absorption from the intestinal tract decreases with increasing molecular weight of the poly-AMPS. This is explained below.

The table presents the plasma clearance via only the small intestines of the rabbit for a range of substances in vivo as a measure for the permeability of the small intestines (Loehry et al 1970). These authors conclude that the molecular weight is a controlling parameter for the uptake rate of substances from the small intestines into the blood. This is also supported by the computational approaches of Subramanian and Kitchen (2006) for modelling human intestinal absorption and permeability. Permeability decreases with increasing molecular weight in the mathematical models of these latter authors.

Substance	*Clearance (ml/min)*	*Molecular Weight*
Urea	1·8	60
Creatinine	0·51	113
Fructose	0·31	180
Vitamin B_{12}	0·053	1,000
Inulin	0·028	5,500
PVP	0·007	33,000

Table *Intestinal clearance values*

In this way poly-AMPS will be less absorbed from the small intestines into the blood with increasing molecular weight. Still absorption of the cations may take place, that are in equilibrium with the negatively charged anionic groups (sulfonic acid groups) in the intestinal fluid. Because poly-AMPS remains in the intestines, toxic systemic effects caused by poly-AMPS seem to be less probable with increasing molecular weight of poly-AMPS.

Considering the above reasoning it is concluded that the drinking water standard of mono-AMPS.NH_4 may be applied to poly-AMPS.NH_4. In this way the drinking water standard of poly-AMPS is equal to that of mono-AMPS, that is 11 mg AMPS per litre drinking water (rounded to two digits).

5. References

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ECHA 2020b, Dossier AMPS sodium salt: https://echa.europa.eu/registration-dossier/-/registered-dossier/15188.

EPA 2019. Predictive Models and Tools for Assessing Chemicals under the Toxic Substances Control Act (TSCA). https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

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Nielsen CU, Bjerg M, Ulaganathan N, Holm R, 2017. Oral and intravenous pharmacokinetics of taurine in sprague-dawley rats: the influence of dose and the possible involvement of the proton-coupled amino acid transporter, PAT1, in oral taurine absorption. Physiol Rep. 2017 Oct;5(19):e13467.

Subramanian G, Kitchen DB, 2006. Computational approaches for modelling human intestinal absorption and permeability. J Mol Model. 12(5):577-89.

Appendix D
Derivation of the indicative drinking water target value for HAPNQ

Summary

The ECHA database on 4-methoxy-N-(3-N,N-dimethylaminopropyl)naphta (CAS# 276878-97-8, HAPNQ) has been used as the basic source for toxicity information. The lowest NOAEL was selected from a range of toxicological endpoints in studies with rodents. The lowest NOAEL was found to be 473 mg/kg-bw/day related to the oral feed study for a period of 4 weeks in rats. This NOAEL was taken as starting point for deriving a maximum concentration in drinking water. For deriving a DNEL (Derived No Effect Level) of HAPNQ for the general population, the following assessment factors were considered:

- subacute to chronic duration (6)
- interspecies variability (10)
- intraspecies variability (10)

Applying above assessment factors to the lowest NOAEL results into a DNEL for the general population of (473/(6*10*10) =) 0,79 mg/kg-bw/day. In addition, the daily dose via drinking water uptake (2 litres at 70 kg bodyweight per day) may not exceed 20% of the DNEL of the general population.
This results in a drinking water limit of (20%*70*0,79/2 =) 5,5 mg HAPNQ per litre (rounded to two digits.

1. Introduction

HAPNQ, 4-methoxy-N-(3-N,N-dimethylaminopropyl)naphta (CAS# 276878-97-8), is a chemical with fluorescent properties. The chemical can be co-polymerized with various water-soluble compounds such as acrylamide, acrylic acid and other unsaturated monomers to form fluorescent polymers. With the characteristics of large molecular weight, strong fluorescence and high sensitivity, its detection sensitivity can reach 100 ppb. This provides extremely favorable conditions for accurate assessment, automatic detection and automatic control of water systems.

The molecular weight of the monomer amounts is about 427,5. The backbone of HAPNQ is presented in figure 1.

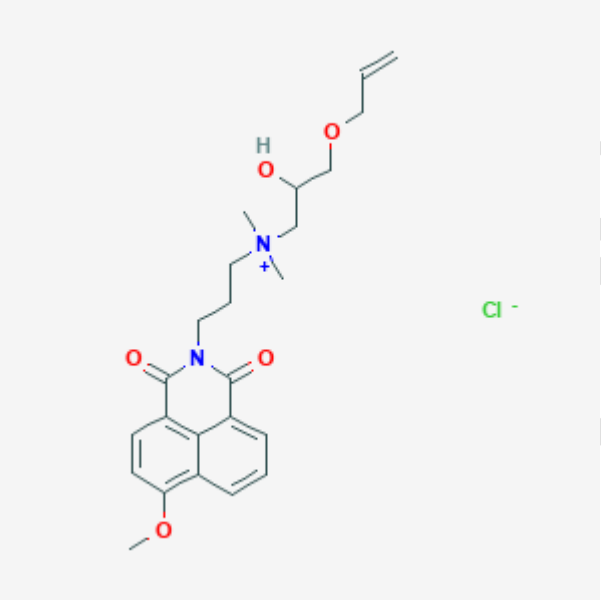

Fig 1: Back bone HAPNQ monomer

As a constituent of the TRC233 polymer, HAPNQ may be discharged with the bleed of a cooling system into surface water.
River water may be used as a raw material for drinking water. The technical processes for the preparation of drinking water are not always able to remove completely polymer from the drinking water. This note reviews the existing toxicological information of HAPNQ with the aim to derive a limit for TRC233 polymer in drinking water.

2. Toxicological information on HAPNQ (CAS# 276878-97-8)

The toxicology of HAPNQ has been studied. Public available information is registered in the ECHA database (https://echa.europa.eu/registration-dossier/-/registered-dossier/2939) and is summarized in the following paragraphs:

2.1 Acute oral toxicity (rat)

The acute oral toxicity was studied in rats for HAPNQ. The LD50 appeared to be larger than 2 grams per kg bodyweight.

2.2 Acute dermal toxicity (rabbit)

The acute dermal toxicity was studied in rats for HAPNQ. The LD50 appeared to be larger than 2 grams per kg bodyweight.

2.3 Acute inhalation toxicity (LC50 4 hours)

No references found to this type of study.

2.4 Skin Irritation

Several skin irritation studies on rabbits were done in accordance with OECD Guideline 404. All studies show no skin irritation potential.

2.5 Skin sensitisation

HAPNQ was tested for skin sensitisation in the mice using Local Lymph Node Assays. HAPNQ showed no sensitising potential in the LLNA.

2.6 Repeated dose toxicity (oral)

The repeated dose toxicity of HAPNQ to rats has been tested in accordance with the OECD Guideline 407 study with substance application via oral feed for 28 days to examine the effect of the test substance on mineral homeostasis.
The oral administration (gavage) of the test substance to rats for a period of 28 consecutive days at dose levels of 12, 71, and 473 mg/kg/day produced no treatment-related changes in the parameters measured. The NOAEL of 473 mg/kg/day was reported.

2.7 Repeated dose toxicity by inhalation

No references found to this type of study.

2.8 Repeated dose toxicity by dermal exposure (bath water)

No references found to this type of study.

2.9 Genetic toxicity in vitro

Genetic toxicity of HAPNQ was tested in vitro in a chromosome aberration assay (OECD Guideline 473 and EU method B.10). These tests are able to detect point and frameshift mutations and chromosome breaks. No mutagenic activity was observed in these in vitro tests.

2.10 Genetic toxicity in vivo

No references found to this type of study.

2.11 Carcinogenicity

Carcinogenicity studies have not been performed for HAPNQ. Carcinogenicity studies are not considered to be relevant considering the chemical structure and the absence of any mutagenic activity in experimental studies in vitro and in vivo [ECHA, 2020].
Toxtree indicates HAPNQ negative for nongenotoxic carcinogenicity.

2.12 Reproductive and developmental toxicity

No references found to this type of study. Toxtree indicates HAPNQ negative for genotoxic carcinogenicity.

3. Derivation of a drinking water limit for HAPNQ

In the 28-day repeated dose study in rats the highest dose without any effect appeared to be 473 mg/kg-bw/day, based on the repeated dose oral toxicity.

In the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2.1 November 2012) has been stated how such an acute NOAEL should be translated to a Derived No Effective Level for consumers via extrapolation assessment factors:

rat to human	10
general population	10
28 days to 2 year rat	6

This results into a DNEL of 473 / (10*10*6) = 0,79 mg/kg-bw/day for humans.

There is an additional limitation in the Netherlands for drinking water. Drinking water may not contribute more than 20% of the total DNEL to the daily body burden in a daily drinking water volume of 2 litres at a body weight of 70 kg. This means that the total mass of HAPNQ in drinking water may not exceed 20%*70*0,79/2 = 5,5 mg/litre.

4. References

ECHA, 2020. Dossier HAPNQ: https://echa.europa.eu/registration-dossier/-/registered-dossier/2939.

Toxtree. "Estimation of Toxic Hazard – A Decision Tree Approach"; version 3.1.0.1851, www.ideaconsult.net.

Appendix E
Flowcharts for the derivation of the TDI

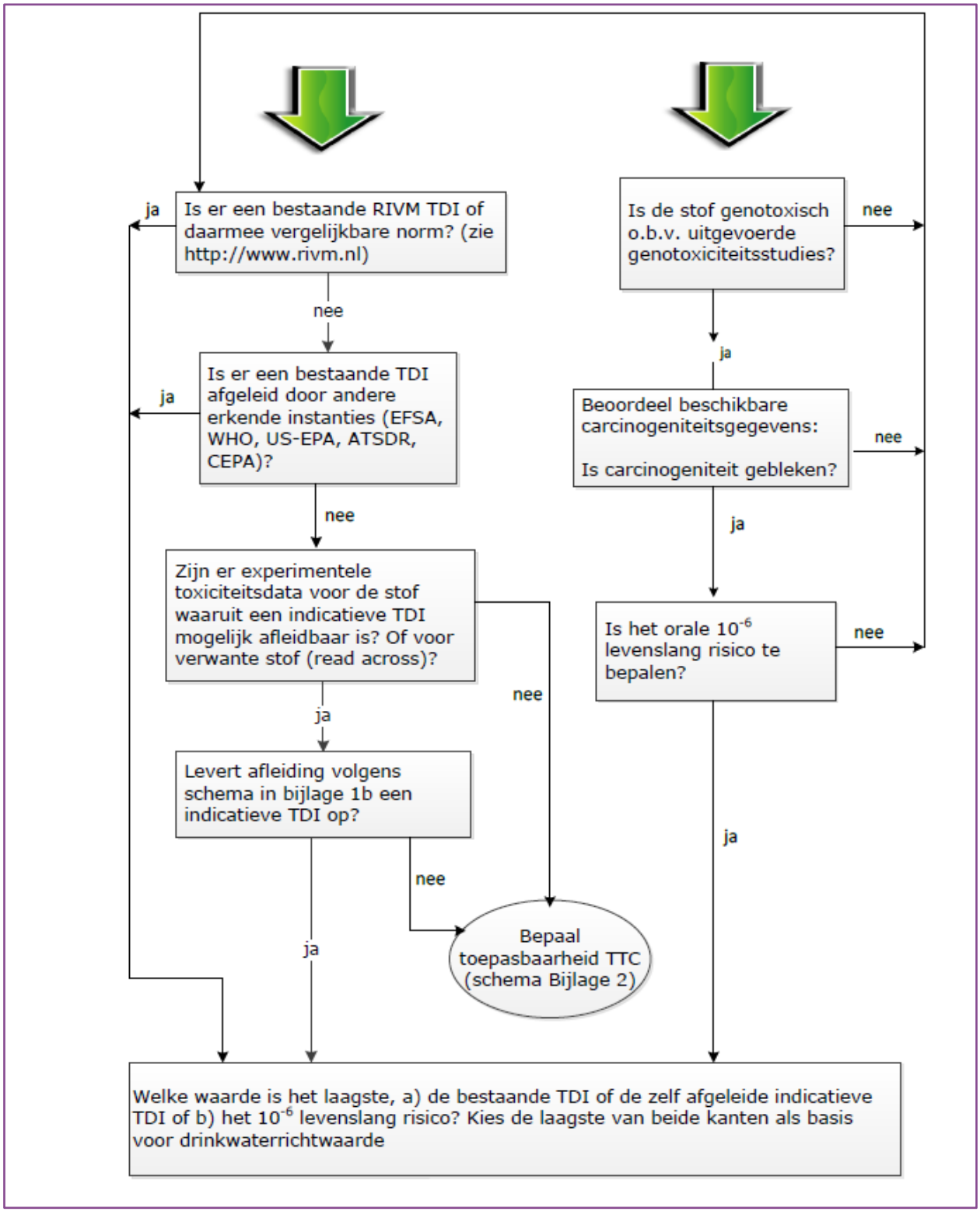

Figure E.1 Flow diagram to determine the necessity of derivation of the TDI

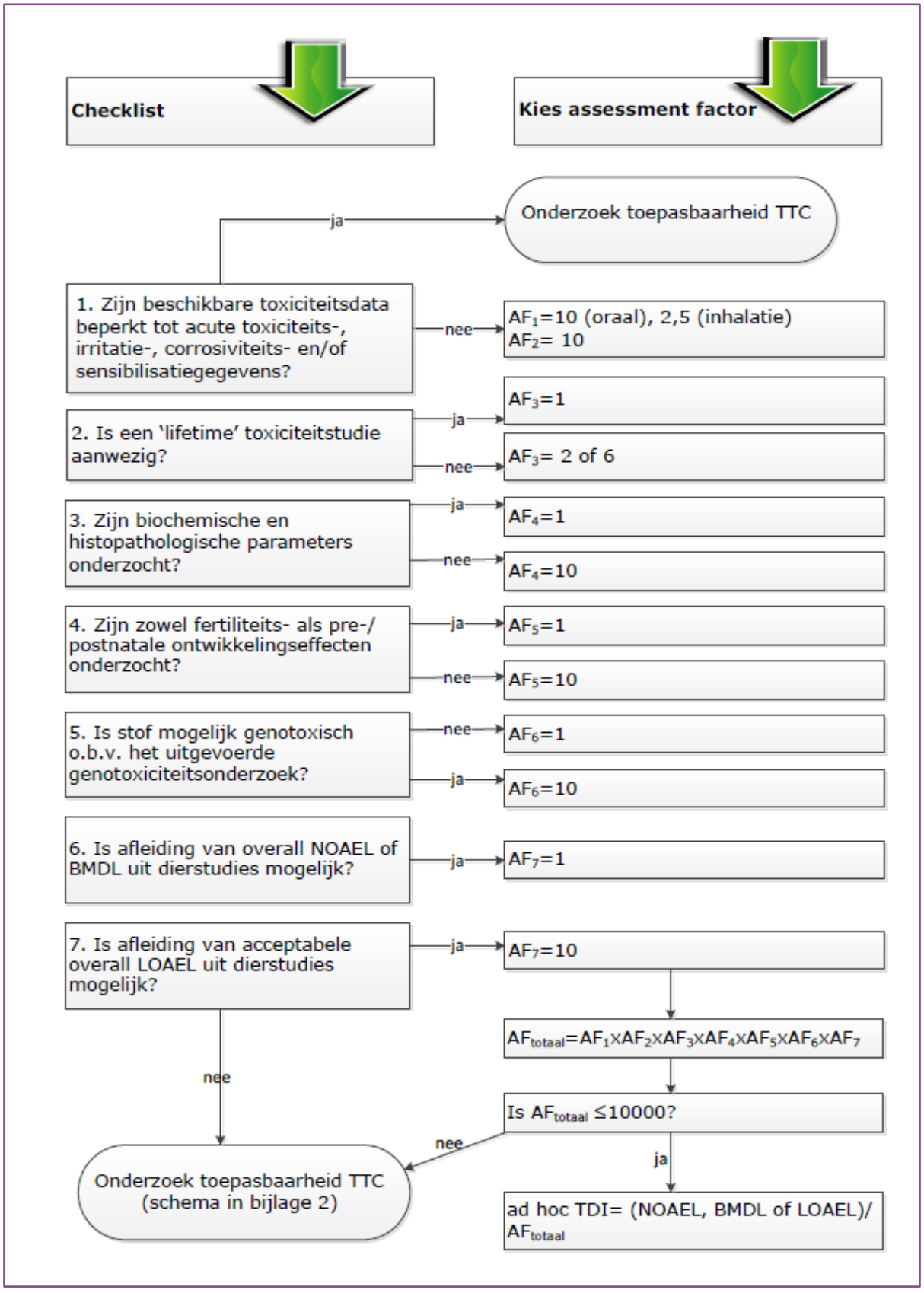

Figure E.2 Flow diagram to derive the TDI for a chemical using assessment factors

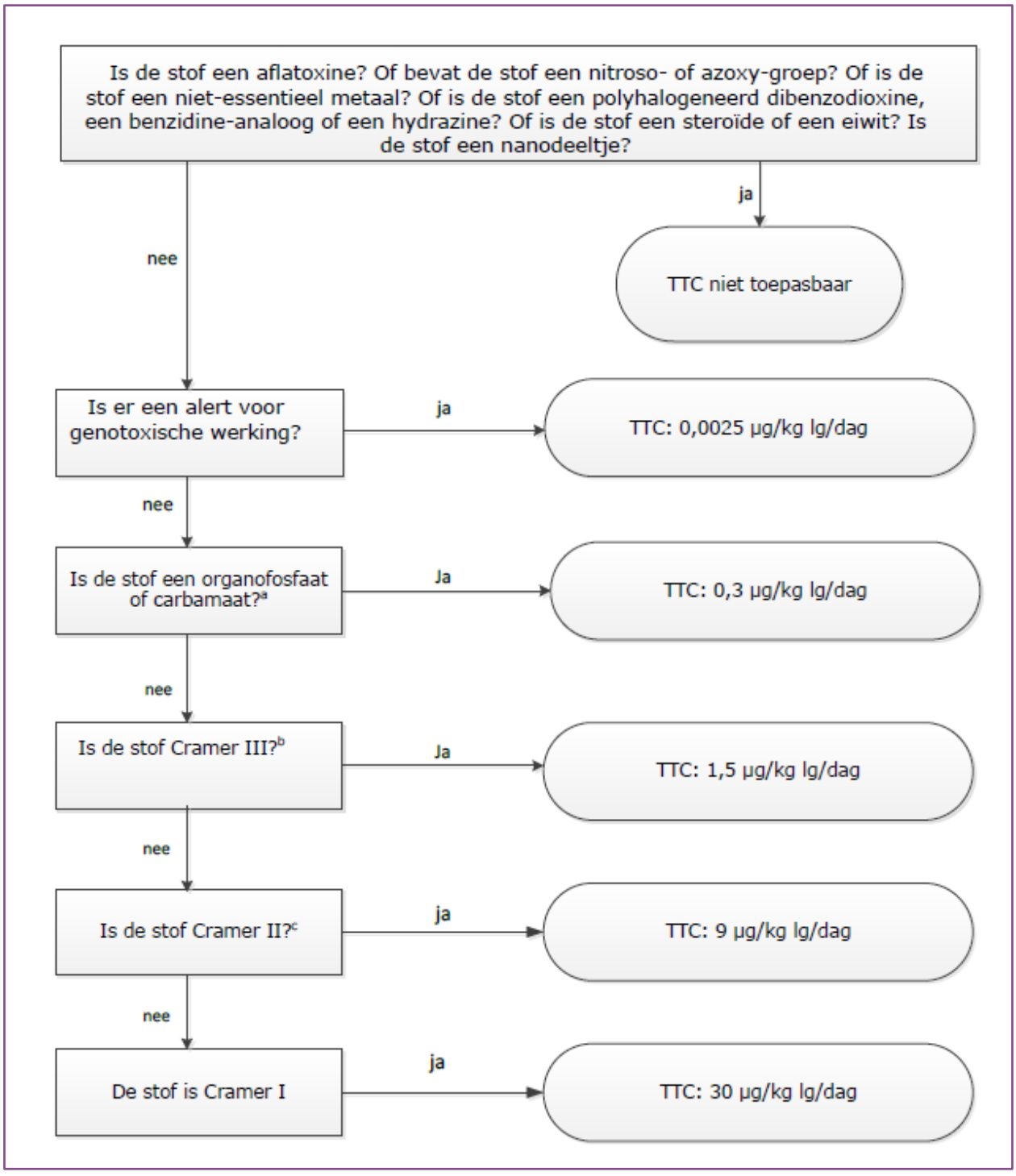

Figure E.3 Flow diagram to derive the TDI based on generic properties