

Bijlage A. Toelichting op de wijzigingsaanvraag 2-hydroxyethyl methacrylaat (HEMA) en methacrylzuur

1 Stoffen

Door het gebruik van HEMA op Chemelot is het mogelijk dat deze stof via het procesafvalwater geloosd wordt richting IAZI. Verwacht wordt dat een afbraakproduct van HEMA de stof methacrylzuur is. Omdat methacrylzuur niet is opgenomen in bijlage 4 van de vigerende vergunning, is deze stof meegenomen ter beoordeling in deze aanvraag.

De stoffen zijn biologisch goed afbreekbaar, waardoor de IAZI als BBT aangemerkt kan worden.

2 Toepassing en gebruik

De stof HEMA dient als toevoeging voor de vorming van een co-polymeer van ethyleen en HEMA, waardoor een nieuw type LDPE eindproduct kan worden geproduceerd. Uiteindelijk is het de bedoeling om van dit type LDPE ca. 40 kton/jaar te produceren. Omdat HEMA wordt ingebouwd in het eindproduct tijdens de polymerisatie zou er theoretisch geen lozing van moeten zijn. Worst case is uit onderzoek berekend dat er jaarlijks maximaal 196 kg HEMA richting IAZI geloosd kan worden. Omdat methacrylzuur een afbraakproduct is, is deze ook beoordeeld en wordt deze stof meegenomen in deze wijzigingsaanvraag.

3 ABM2016 indeling

De stof 2-hydroxyethyl methacrylaat (CAS# 868-77-9) wordt middels de ABM toets ingedeeld als B5. De gegevens van HEMA voor de ABM2016 toetsing zijn te vinden in bijlage A1.

De stof methacrylzuur (CAS# 79-41-4) wordt middels de ABM toets ingedeeld als B3. De gegevens van methacrylzuur voor de ABM toetsing zijn te vinden in bijlage A1.

4 Sommatie

HEMA (CAS# 868-77-9) is een nieuwe stof op de Chemelot locatie. De totale jaarlijkse vracht zal maximaal 196 kg richting IAZI betreffen. Ervan uitgaande dat HEMA wordt afgebroken naar methacrylzuur voor maximaal 65 massa%, zal de totale jaarlijkse vracht 127.4 kg richting IAZI zijn.

5 Verwijdering in IAZI en restemissie

HEMA (CAS# 868-77-9) en methacrylzuur (CAS# 79-41-4) zijn "Readily biodegradable" volgens OECD 301C/D testen.

De gerapporteerde afbreekbaarheid voor beide stoffen zijn respectievelijk 92 - 100%¹ en 86%².

Voor de toetsing van de restemissie en de beoordeling van het effect voor het oppervlaktewater zijn de laagste gerapporteerde rendementen aangehouden om worst-case benadering toe te passen.

6 Immissietoets

Voor HEMA zijn door Circle indicatieve normen afgeleid op gebied van ecologie en drinkwater. Voor methacrylzuur is door Circle ook een indicatieve norm voor drinkwater afgeleid. Zie bijlages C1 t/m C3.

In Tabel 6-1 zijn de algemene parameters weergegeven voor het uitvoeren van de immissietoets.

Tabel 6-1, Parameters immissietoets

Parameter	Waarde
Maasdebiet 90-%	20 m3/s
Maximale lozing (scenario 1)	1,4 m3/s effluentdebiet
Gemiddelde lozing (scenario 2)	0,95 m3/s effluentdebiet
Toetsing ecologie acuut (MAC-MKE) =PEC15	Concentratie op 15 meter na lozingspunt
Toetsing ecologie chronisch (JG-MKE) =PEC600	Concentratie op rand mengzone = 600 meter na lozingspunt
Toetsing op waterlichaam (KRW)	Concentratie na volledige menging op monitoringspunt
Drinkwatertoets	Indien geen drinkwater richtwaarde bekend dan toetsing tegen signaleringswaarde voor overige antropogene stoffen van 1 µg/l

De gebruikte normen voor de immissietoets zijn weergegeven in Tabel 6-2. Dit zijn indicatieve normen die nog ter beoordeling naar de WKnwl moeten worden gestuurd. Zie bijlage C1 t/m C3, respectievelijk de afleiding van de MAC-MKE en JG-MKE voor HEMA, de afleiding van de indicatieve drinkwaterrichtwaarde (iDW) voor HEMA, en de afleiding van de iDW voor metacrylzuur.

¹ ECHA disseminated dossier, <https://www.echa.europa.eu> , CAS# 868-77-9

² ECHA disseminated dossier, <https://www.echa.europa.eu> , CAS# 79-41-4

Tabel 6-2, Normen gebruikt bij de immissietoets

Stofnaam	CAS nummer	(i)MAC-MKE $\mu\text{g/l}$	(i)JG-MKE $\mu\text{g/l}$	Achtergrond Concentratie $\mu\text{g/l}$	(i)Drinkwater richtwaarde $\mu\text{g/l}$
2-hydroxyethyl methacrylaat	868-77-9	1000 (Circle)	49 (Circle)	Niet aanwezig in database RWS	1670 (Circle)
methacrylzuur	79-41-4	450 (RIVM)	164 (RIVM)	Niet aanwezig in database RWS	3150 (Circle)

De resultaten van de uitgevoerde immissietoets zijn weergegeven in bijlage A1 (Stoffenlijst - ABM2016 - Immissietoets). Voor de volledigheid zijn de rekensheets van de immissietoetsen opgenomen als bijlage B1.

Conclusie is dat de lozing via het effluent van de IAZI voor de stoffen HEMA en methacrylzuur volgens de immissietoets voldoen in stap 1 voor zowel de ecologische- als voor de drinkwatertoetsing.

7 Advies belanghebbende partijen

Er is advies ingewonnen bij belanghebbende partijen WML, EVIDES en HetWaterlaboratorium. Hun afgestemd advies wordt hieronder onverkort weergegeven:

“Wij hebben de wijzigingsaanvraag, mbt de stoffen HEMA en methylacrylzuur, beoordeeld en hebben hierover verder geen bezwaar of verdere vragen.

Toelichting:

Voor deze stoffen zijn de REACH dossiers doorgenomen en het lijken geen zorgwekkende stoffen voor de drinkwaterproductie. In het effluent liggen de concentraties volgens de ingeschatte afbraak rond 2,5 $\mu\text{g/L}$, dus bij het innamepunt <1 $\mu\text{g/L}$. Methylacrylzuur heeft een volledig toxicologisch dossier en heeft een lage toxiciteit (niet genotoxisch en bij een twee jaar lange blootstelling van ratten aan 2000 $\mu\text{g/L}$ via drinkwater zijn geen relevante effecten gevonden). Voor HEMA is een deel van het dossier ingevuld op basis van read-across vanuit een ander metaboliet van methylacrylzuur. Biologische afbraak is wel met HEMA bepaald en de stof wordt voor 92-100% afgebroken in 14 dagen. De toxiciteit bij kortdurende blootstelling is laag en bij langdurige blootstelling ook op basis van read-across.

Bovendien zijn volgens de Immissietoets de concentratie bij drinkwaterinnamepunten laag, rond 0,2 $\mu\text{g/L}$ en met de afbreekbaarheid nog lager.”

Bijlage

A1 Stoffenlijst update HEMA en methacrylzuur versie 13-6-2024

B1 Rekensheets Immissietoets

C1 Afleiding ecologische toetswaarde HEMA: Milieukwaliteitseisen - 2-Hydroxyethyl methacrylate (HEMA) (CAS#868-77-9) FINAL

C2 Afleiding indicatieve drinkwatertoetswaarde HEMA: iDWN 2-Hydroxyethyl methacrylate (HEMA) (CAS#868-77-9) FINAL

C3 Afleiding indicatieve drinkwatertoetswaarde methacrylzuur: iDWN Methacrylic acid (CAS#79-41-4) FINAL

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Bijlage C1 Afleiding ecologische toetswaarde HEMA: Milieukwaliteitseisen - 2-
Hydroxyethyl methacrylate (HEMA) (CAS#868-77-9) FINAL

Notitie / Memo

HaskoningDHV Nederland B.V.
Industry & Buildings

Aan: Sitech IAZI bv

Van:

Datum: 15 mei 2023

Kopie:

Ons kenmerk: BJ1982IBNT001F01

Classificatie: Alleen voor intern gebruik

Gecontroleerd door

Onderwerp: Milieukwaliteitseisen voor 2-Hydroxyethyl methacrylaat (CAS# 868-77-9)

Bij de productie van HDPE wordt Hydroxyethyl methacrylaat (verder HEMA; CAS# 868-77-9) als additief gebruikt. De toepassing van HEMA in systemen op de site Chemelot leidt tot lozing op de IAZI en tot lozing op de Grensmaas. De mogelijke effecten van de lozing van HEMA op de functies van de Grensmaas moeten geëvalueerd worden met behulp van de immissie-toets. Om deze toetsing mogelijk te maken zijn ecologische waterkwaliteitsnormen en de drinkwater-richtwaarde noodzakelijk. Omdat er momenteel geen ecologische waterkwaliteitsnormen beschikbaar zijn, worden hiertoe in deze rapportage voorstellen gedaan.

Datamining

In eerste instantie is de website van het RIVM geraadpleegd of voor de stof al normen beschikbaar zijn. Hierbij is gezocht op het CAS#. Vervolgens zijn de databases van ECHA en US-EPA (Ecotox) geraadpleegd aan de hand van het CAS#. De stof is geregistreerd onder REACH. Aanvullend is gezocht naar een stof-specifiek IUCLID dan wel OECD-rapport en is een brede screening van openbare literatuur uitgevoerd. De resultaten van dit literatuuronderzoek staan in Bijlage 1 (stofgegevens) en in Bijlage 2 (ecotoxicologische data) weergegeven.

Voorstel voor milieukwaliteitseisen

De voorgestelde milieukwaliteitseisen voor HEMA zijn afgeleid op basis van experimentele data en de toepassing van veiligheidsfactoren. De indicatieve JG-MKN respectievelijk de indicatieve MAC-MKN zijn afgeleid conform RIVM Handleiding voor het afleiden van indicatieve milieurisicogrenzen (Deel 5. Afleiding risicogrenzen per compartiment, 2022). In bijlage 3 is het stappenschema voor de afleiding van de iJG-MKN uitgewerkt. In bijlage 4 is het uitgewerkte stappenschema voor de afleiding van de iMAC-MKN weergegeven.

De afgeleide waarden voor Hydroxyethyl methacrylaat (HEMA; (CAS# 868-77-9) zijn:

iMAC-MKN_{zoet} = 1,0 mg/L

iJG-MKN_{zoet} = 0,049 mg/L

Referenties

ECHA database, <https://www.echa.europa.eu> , CAS# 868-77-9), geraadpleegd op 13 februari 2023

Ecotox database, <https://cpub.epa.gov/ecotox>, CAS# 868-77-9) geraadpleegd op 13 februari 2023

OECD SIDS 2001, 2-Hydroxyethyl methylacrylate CAS No. 868-77-9

<https://hpvchemicals.oecd.org/ui/handler.axd?id=6be3682f-b427-4abd-9278-8b9b147cfc15>, gedownload op 14 februari 2023

RIVM, 2022. "Handleiding voor de afleiding van indicatieve milieurisicogrenzen Deel 5: Afleiding van risicogrenzen per compartiment – versie 1.0"

RIVM, 2022. "Handleiding voor het afleiden van indicatieve milieurisicogrenzen Deel 4. Ecotoxiciteit: verzameling, selectie en rapportage van gegevens – versie 1.0"

RIVM, 2015. "Handleiding voor de afleiding van indicatieve milieurisicogrenzen"; L.R.M. de Poorter et al, RIVM-rapport 2015-0057.

Bijlage 1 Identificatie, classificatie, fysische chemische eigenschappen en milieugedrag van 2-Hydroxyethyl methacrylaat (HEMA)

Identificatie en Classificatie

Parameter	Waarde
Stofnaam	2-Hydroxyethyl methacrylaat
IUPAC-naam	2-hydroxyethyl methacrylate
Synoniemen	2-HEMA
CAS-nummer	868-77-9
Stofgroep Epiwin	Methacrylaten
Geharmoniseerde classificatie	Ja, alleen voor humane gezondheid
Relevante zaken m.b.t. geharmoniseerde classificatie	H315, H317, H319 (Veroorzaakt huid- en ernstige oog irritatie en kan huidallergie veroorzaken) Zelfclassificatie: H317, H320 (Veroorzaakt oogirritatie en kan huidallergie veroorzaken)
REACH / Zeer Zorgwekkende Stof	Nee
Molecuulformule	C ₆ H ₁₀ O ₃
Smiles	O=C(OCCO)C(=C)C

Fysisch-Chemische eigenschappen

Parameter	Waarde	Opmerking	Ref.
Molecuulgewicht (g/mol)	130,14		EpiWin
Smeltpunt (°C)	-99	1013 hPa	ECHA
Kookpunt (°C)	213	1013 hPa	ECHA
Oplosbaarheid in water (g/L)	100	25 °C	ECHA
Log Kow	0,42	25 °C (OECD 107)	ECHA
Dampspanning (kPa)	0,008	20 °C, niet vluchtig	ECHA
Henri-coefficient (Pa.m ³ /mol)	9,720E-004		ECHA
Zuurconstante (pKa)	-		

Milieugedrag

Parameter	Waarde	Opmerking	Ref
Afbreekbaarheid	Makkelijk afbreekbaar: OECD 301C (14 d) OECD 301E (21 d) OECD 301D (28 d)		ECHA
DT50 hydrolyse	10,9 dagen	pH = 9, 25 °C	ECHA
DT50 water/sediment	-		
Log K _{oc} (L/kg)	1,46 (MCI)	Lage adsorptiecapaciteit vanwege de lage K _{ow} (0,42)	EpiWin
BCF	3,16 L/kg ww		EpiWin

2-Hydroxyethyl methacrylaat is zeer goed oplosbaar in water, de waarde voor de log K_{ow} is hiermee in overeenstemming. De voorspelde waarde voor K_{oc} is laag, de stof wordt daarom verwacht erg mobiel te zijn in de bodem

Bijlage 2 Overzicht ecotoxiciteitsgegevens voor 2-Hydroxyethyl methacrylaat (HEMA, CAS# 868-77-9)

Voor 2-Hydroxyethyl methacrylaat zijn enkele ecotoxicologische gegevens beschikbaar, zowel in de ECHA-database als in de Ecotoxicity database van de EPA. In de laatste was geen andere informatie te vinden ten opzichte van de ECHA-database. De OECD SIDS rapportage (2001) over deze stof is eveneens geraadpleegd, maar ook hier was geen extra informatie aanwezig.

Daarom is verder gezocht in de publieke literatuur via Google en Google Scholar met stofnaam, groepsnaam, Cas nummer, aquatic, ecotoxicity, fish, invertebrate, daphnia en algae, aquatic. Geen additionele bruikbare informatie kon worden gevonden.

Grijs gearceerde eindpunten zijn geselecteerd voor het afleiden van de indicatieve milieukwaliteitseisen.

Overzicht acute ecotoxiciteitsgegevens

Soort	Blootstellings-duur	Eindpunt	Waarde (mg/L)	Stof	Klimisch score ¹	Bron
Bacteriën						
<i>Pseudomonas fluorescens</i>	16 h	EC0	>3000	HEMA (zuiverheid 99,6%)	2	ECHA
<i>Photobacterium phosphoreum</i>	-	EC50	2204	HEMA	4	ECHA
-	3h	EC50	8560	HEMA	4	ECHA
Algen						
<i>Raphidocelis subcapitata</i>	72 h	EC50	345	HEMA (zuiverheid 97,2%)	1	ECHA
Kreeftachtigen						
<i>Daphnia magna</i>	48 h	EC50	380	HEMA (zuiverheid 97,2%)	1	ECHA
Vissen						
<i>Oryzias latipes</i>	96 h	LC50	>100	HEMA (zuiverheid 98,9%)	1	ECHA
<i>Oryzias latipes</i>	14 d	LC50	>100	HEMA (zuiverheid 97,2%)	1	ECHA
<i>Pimephales promelas</i>	96 h	LC50	227	HEMA (zuiverheid 98,5%)	2	ECHA EPA Ecotox
<i>Leucidus idus</i>	48 h	LC50	360	HEMA	4	ECHA
<i>Carassius auratus</i>	72 h	LC50	374,5	HEMA	4	ECHA

¹ Klimisch score overgenomen uit ECHA dossier
15 mei 2023

Overzicht chronische ecotoxiciteitsgegevens

Soort	Blootstellings- duur	Eindpunt	Waarde (mg/L)	Stof	Klimisch score ²	Bron
Bacteriën						
Geen gegevens						
Algen						
<i>Raphidocelis subcapitata</i>	72 h	NOEC	160	HEMA (zuiverheid 97,2%)	1	ECHA
Kreeftachtigen						
<i>Daphnia magna</i>	21 d	NOEC	24,1	HEMA (zuiverheid 97,2%)	1	ECHA
Vissen						
Geen gegevens						

² Klimisch score overgenomen uit ECHA dossier
15 mei 2023

Bijlage 3 Uitwerking stappenschema afleiden iJG-MKN_{zoet, eco}

Stappenschema 2 iJG-MKN_{zoet, eco}

Nr.	Vraag / Statement	Antw.	Conclusie / actie	Ga naar
1	Is er een gedegen Nederlandse JG-MKN _{zoet} beschikbaar?	Ja	iJG-MKN wordt niet afgeleid	STOP
		Nee		2
2	Is er een gedegen MTR _{zoet} beschikbaar?	Ja		3
		Nee		4
3	Voedselketenroute afgedekt door MTR _{zoet} ?	Ja	iJG-MKN _{zoet} wordt niet afgeleid	STOP
		Nee		4
4	Zijn er experimentele ecotoxiciteitsdata voor water?	Ja		6
		Nee		5
5	Is het gebruik van QSAR's mogelijk? Overleg met een expert.	Ja		6
		Nee	iJG-MKN _{zoet, eco} kan niet worden afgeleid	STOP
6	Data voor:	Alleen acuut	iJG-MKN _{zoet, eco} iJG-MKN _{zoet, eco-acuut} = $L(E)C50_{min}/AF$	12
		Alleen chronisch	iJG-MKN _{zoet, eco-chronisch} = $NOEC_{min}/AF$	11
		Acuut en chronisch	Bepaal beide hierboven genoemde waarden	7
7	Dataset voor gehele acute basisset	Ja		8
		Nee		11
8	NOEC voor tenminste kreeftachtige of vis én NOEC beschikbaar voor dezelfde soort als $L(E)C50_{min}$	Ja ^a	kies iJG-MKN _{zoet, eco-chronisch}	9
		Nee	iJG-MKN _{zoet, eco} = laagste van iJG-MKN _{zoet, eco-acuut} en iJG-MKN _{zoet, eco-chronisch}	12
9	Potentieel gevoelige groep getest?	Nee	iJG-MKN _{zoet, eco} = iJG-MKN _{zoet, eco-chronisch}	12
		Ja	iJG-MKN _{zoet, eco} = iJG-MKN _{zoet, eco-chronisch} x 10	12
10	NOEC beschikbaar voor soort met $L(E)C50_{min}$	Ja		11
		Nee	iJG-MKN _{zoet, -eco} = laagste van iJG-MKN _{zoet, eco-acuut} en iJG-MKN _{zoet, eco-chronisch}	12
11	Data voor tenminste gehele chronische dataset én potentieel gevoelige groep getest?	Ja ^a	iJG-MKN _{zoet, eco} = iJG-MKN _{zoet, eco-chronisch} x 10	12
		Nee	iJG-MKN _{zoet, eco} = iJG-MKN _{zoet, eco-chronisch}	12
12	iJG-MKN _{zout, eco} = iJG-MKN _{zoet, eco} /10			13
13	Gebruik iJG-MKN _{zoet, eco} voor de selectie van de iJG-MKN _{zoet} Gebruik iJG-MKN _{zout, eco} voor de selectie van de iJG-MKN _{zout}			

a: Als de NOEC_{min} of $L(E)10$ hoger is dan de $L(E)50_{min}$, raadpleeg dan de guidance voor gedegen normen om een gemotiveerde keuze te maken voor de uiteindelijke AF.

Resultaat voor afleiding iJG-MKN_{zoet, eco} voor 2-Hydroxyethyl methacrylaat (CAS# 868-77-9)

Nr.	Antw.	Conclusie / actie	Ga naar
1	Nee		2
2	Nee		4
3			
4	Ja		6
5	-		
6	Acuut en chronisch	iJG-MKN _{zoet, eco- acuut} = $L(E)C_{50min}/AF =$ $(>)100 / 1000 =$ 0,10 mg/L iJG-MKN _{zoet, eco- chronisch} = $NOEC_{min}/AF =$ $24,1 / 500 =$ 0,049 mg/L	7
7	Ja		8
8	Nee	Laagste = iJG-MKN _{zoet, eco-chronisch}	12
9	-		
10	-		
11	-		
12	iJGMKN _{zout,eco} = 0,049 mg/L/10 = 4,9 µg/L		13
13	De iJG-MKN _{zoet} is afgeleid als 0,049 mg/L (afgerond op twee significante cijfers) De iJG-MKN _{zout} is afgeleid als 4,9 µg/L (afgerond op twee significante cijfers)		

Er zijn gegevens beschikbaar voor de gehele acute basisset en voor twee soorten van de chronische basisset, zie ook bijlage 1. De laagste waarde voor $L(E)C_{50min}$ is de acute toxiciteit voor *Oryzias latipes*. De geleedpotige *Daphnia magna* was het meest gevoelig in een chronische test. Beide studies zijn als Klimisch 1 beoordeeld.

De gehanteerde assessment factoren zijn overgenomen van tabel 1 in 2.2.2 van het RIVM Handleiding voor het afleiden van indicatieve milieurisicogrenzen Deel 5 (2022).

Doorvergiftiging in de voedselketen is niet getriggerd vanwege $\log K_{ow} < 3$.

Bijlage 4 Uitwerking stappenschema afleiden iMAC-MKN_{zoet, eco}

Stappenschema 3 iMAC-MKN_{zoet, eco}

Nr.	Vraag / Statement	Antw.	Conclusie / actie	Ga naar
1	Is er een gedegen Nederlandse MAC-MKN of MAC _{eco,zoet} beschikbaar?	Ja	iMAC-MKN wordt niet afgeleid	STOP
		Nee		2
2	Zijn er experimentele ecotoxiciteitsdata voor water?	Ja		4
		Nee		3
3	Is het gebruik van QSAR's mogelijk? Overleg met een expert.	Ja		4
		Nee	iMAC-MKN wordt niet afgeleid	STOP
4	Bereken iMAC-MKN _{zoet, eco}		iMAC-MKN _{zoet, eco} = $L(E)C50_{min}/AF$	5
5	iMAC-MKN _{zout, eco} = iMAC-MKN _{zoet, eco} / 10			

Resultaat voor afleiding iMAC-MKN_{zoet, eco} voor 2-Hydroxyethyl methacrylaat (CAS# 868-77-9)

Stap	Antwoord	Conclusie actie	Ga naar
1	Nee		2
2	Ja		4
3	-		
4	Bereken iMAC-MKN _{zoet, eco}	iMAC-MKN _{zoet, eco} = $L(E)C50_{min}/AF = (>)100 / 100 = 1,0 \text{ mg/L}$	5
	De iMAC-MKN _{zoet} is afgeleid als 1,0 mg/L (afgerond op twee significante cijfers)		
5	De iMAC-MKN _{zout} is afgeleid als $1,0/10 = 0,1 \text{ mg/L}$ (afgerond op twee significante cijfers)		

Er zijn acute ecotoxiciteitsgegevens beschikbaar voor de basisgroepen algen, kreeftachtigen en vissen, zie ook bijlage 1. De laagste waarde voor $L(E)C50_{min}$ is de acute toxiciteit voor de vis *Oryzias latipes*, zie ook bijlage 1

Op grond van tabel 2 onder sectie 2.3 van de RIVM Handleiding voor het afleiden van indicatieve milieurisicogrenzen Deel 5, bedraagt de AF 100.

Bijlage C2 Afleiding indicatieve drinkwatertoetswaarde HEMA: iDWN 2-Hydroxyethyl methacrylate (HEMA) (CAS#868-77-9) FINAL

REPORT

Derivation of the indicative Drinking Water Target Value for 2-hydroxyethyl methacrylate (CAS# 868-77-9)

Client: Sitech Services B.V.

Reference: BJ1982I&BRP001F01

Status: Final/01

Date: 22 May 2024

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Document title: Derivation of the indicative Drinking Water Target Value for 2-hydroxyethyl methacrylate (CAS# 868-77-9)

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Appendices

1.	Testing
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Executive Summary

Royal HaskoningDHV was retained by Sitech IAZI bv to derive substance specific water quality standards for 2-Hydroxyethyl methacrylate (CAS# 868-77-9) using the guidance documents. The substance is used as an additive.

There is information available about adverse effects 2-Hydroxyethyl methacrylate (CAS# 868-77-9), the indicative drinking water target value is derived from the available toxicological data. The proposed value for the indicative drinking water target value is set at 1.67 mg/L.

Sitech IAZI bv requests the Wetenschappelijke Klankbordgroep normstelling water en lucht to evaluate and approve proposed indicative values for water quality standards as summarized in below table.

Table 1 Proposed indicative drinking water target values

Parameter	Proposed Indicative Drinking Water Target Value in mg/L
2-Hydroxyethyl methacrylate (CAS# 868-77-9)	1.67

1 Introduction

1.1 Preamble

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.

Present wastewater discharge permit holds an obligation to assess the potential risk of the discharge of 2-Hydroxyethyl methacrylate (CAS# 868-77-9) regarding the downstream withdrawal of surface water of the river Meuse for the preparation of drinking water.

The potential impact of the discharge of containing 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 regarding aquatic ecosystems and the drinking water preparation functions are relevant. Royal HaskoningDHV was asked by Sitech to derive a substance specific drinking water target value for 2-Hydroxyethyl methacrylate (CAS# 868-77-9) using the formal guidance document [RIVM, 2017]. This report describes results of literature research and proposes values for water quality standards for this substance.

1.2 Methodology and data mining

The Dutch National Institute for Public Health and the Environment compiled a formal guidance on the derivation of substance specific indicative drinking water parameters [RIVM, 2017], which aligns with the procedures of the European Commission [EC, 2018]. This guidance is used to derive the drinking water target value for 2-Hydroxyethyl methacrylate (CAS# 868-77-9).

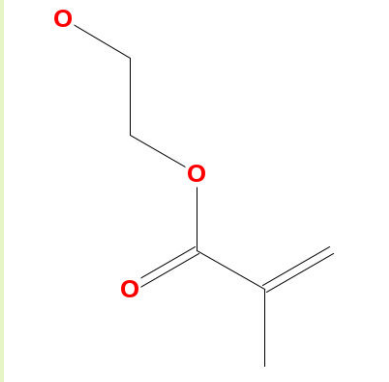
Data of existing evaluations were used as a starting point. As there is no acceptable daily intake (ADI) or tolerable daily intake (TDI) for 2-Hydroxyethyl methacrylate (CAS# 868-77-9) derived by a recognized agency, Royal HaskoningDHV executed an online literature search to compile a dataset with relevant physico-chemical properties and toxicological endpoints, using CAS# 868-77-9. Reviewed sources are:

- RIVM, Normen | Risico's van stoffen (rivm.nl)
- ECHA database, Startpagina - ECHA (europa.eu)
- US-EPA Ecotox database, Ecotoxicology Database | US EPA
- US-EPA IRIS (Integrated Risk Information System | US EPA)
- EPA PRTV (Provisional Peer-Reviewed Toxicity Values (PPRTVs) | US EPA)
- EPA Comptox (CompTox Chemicals Dashboard (epa.gov)
- EPA Regional screening levels (Regional Screening Levels (RSLs) | US EPA)
- EFSA | Science, safe food, sustainability (europa.eu)
- WHO drinking water guidelines (WHO) Guidelines for drinking-water quality: fourth edition incorporating the first and second addenda (who.int)
- PubChem (nih.gov))
- Generic search on the internet in public literature
- Reports provided by the supplier of the chemical

All available toxicity studies were summarized in overviews, that are included in the Appendices to this report. These overviews contain information on species characteristics, test conditions and endpoints.

2 Properties of 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Table 2 Overview of identifiers for 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Parameter	Value
Substance name	2-Hydroxyethyl methacrylate
IUPAC name	2-Hydroxyethyl methacrylate
Synonyms	2- 2-Hydroxyethyl methacrylate
CAS number	868-77-9
EINECS number	212-782-2
Chemical group according to EPIwin	Methacrylates
Cramer class ^{1, 2}	Class I
Harmonized classification	Index number 607-124-00-X Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1
Substance of very high concern	No
Molecule formula	C ₆ H ₁₀ O ₃
Smiles	<chem>CC(=C)C(=O)OCCO</chem>
Molecule structure	

¹

Class I Structures and related data suggest a low order of oral toxicity. If combined with low human exposure, require a low priority for investigation

Class II Less clearly innocuous than Class I, but no firm indication of toxicity or the lack thereof

Class III Structure and related data permit no initial presumptions of safety or may suggest significant toxicity. These substances deserve the highest priority for investigation.

² 1. G.M. Cramer and R.A. Ford Estimation of toxic hazard - a decision tree approach. Food and Cosmetics Toxicology, Volume 16, Issue 6, December 1978, Page 255-276.

2. G. Patlewicz, N.Jeliazkova, R.J. Safford, A.P. Worth, B. Aleksiev. An evaluation of implementation of the Cramer classification scheme in the Toxtree software. SAR and QSAR in Environmental Research. Vol. 19, Nos. 5-6, July-September 2008, Page 495-524.

3. C. Munro, R.A. Ford, E. Kennepohl, J.G. Sprenger. Correlation of Structural class with no-observed-effect levels: proposal for establishing a threshold of concern. Food and Chemical Technology 34 (1996), Page 829-867.

2.1 Physico-chemical properties

Table 3 shows an overview of physico-chemical properties for 2-Hydroxyethyl methacrylate (CAS# 868-77-9).

Table 3 Physico-chemical properties of 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Property	Value	Additional information	Reference
Molecular weight (g/mol)	130.14		
Melting point (°C)	-99	1013 hPa	REACH disseminated dossier
Boiling point (°C)	213	1013 hPa	REACH disseminated dossier
Vapor pressure (Pa)	8	20°C, not volatile	REACH disseminated dossier
Water solubility (g/L)	100	25°C	REACH disseminated dossier
Log Kow	0.42	25°C	REACH disseminated dossier
Henry-coëfficiënt (Pa m ³ /mol)	9.720E-004		REACH disseminated dossier
pKa	No data		

2.2 Toxicokinetics

Reliable experimental data exists to demonstrate that 2-Hydroxyethyl methacrylate is rapidly metabolized by a ubiquitous metabolic pathway within the body. 2-Hydroxyethyl methacrylate is metabolised to ethylene glycol and methacrylic acid. There is a high level of confidence based upon experimental data showing that the half-life of 2-Hydroxyethyl methacrylate is in the order of a few minutes. Furthermore, studies in guinea pigs and in mice with 2-Hydroxyethyl methacrylate indicate that most of the administered material is rapidly cleared from the body following metabolism to CO₂ [ECHA].

2.3 Environmental fate

2-Hydroxyethyl methacrylate is highly soluble in water, the value for log Kow is consistent with this. The predicted value for Koc is low, the substance is therefore expected to be highly mobile in soil.

Table 4 Environmental fate of 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Property	Value	Additional information	Reference
Biodegradability	Readily biodegradable		REACH disseminated dossier
DT50 hydrolysis	10.9 days	pH = 9, 25 °C	REACH disseminated dossier
DT50 water/sediment	-		
Log K _{oc} (L/kg)	1.46 (MCI)	Low adsorption capacity due to low Log K _{ow} (0.42)	EpiWin
BCF	3.16 L/kg ww		EpiWin

2.4 Use

2-Hydroxyethyl methacrylate (CAS# 868-77-9) is used as an additive. The use of 2-Hydroxyethyl methacrylate is restricted to professional use only in the EU as of September 2021 (Commission Regulation (EU) 2020/1682 of November 12, 2020 amending Annex III to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products).

3 Derivation of an indicative drinking water target value

3.1 Overview of available toxicity data for 2-Hydroxyethyl methacrylate

The derivation of the drinking water target value starts with the assessment of the acceptable daily intake following the technical guidance [RIVM, 2017]. The latter parameter is subsequently converted into the drinking water target value based on standard values for body weight and daily drinking water consumption

Table 5 Summary of toxicity endpoints for 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Property	Value	Additional information	Reference
Acute oral toxicity	> 5000 mg/kg bw, rat		REACH disseminated dossier
Acute dermal toxicity	> 5000 mg/kg bw, rat	Read across, Hydroxypropyl methacrylate (CAS# 27813-02-1)	REACH disseminated dossier
Acute inhalation toxicity	No data available		REACH disseminated dossier
Skin irritation	Not irritating	Classified acc. Annex VI of Regulation EU 1272/2008 into Skin irrit. 2	REACH disseminated dossier
Eye irritation	Irritating		REACH disseminated dossier
Skin sensitization	Skin sensitiser, human and animal data.	Subcategorization is not possible, high potency excluded	REACH disseminated dossier
Respiratory sensitization	Respiratory sensitiser, human and animal data.	Concluded in the substance evaluation dossier	ECHA SEV

Property	Value	Additional information	Reference
Repeated dose toxicity	NOAEL: 100 mg/kg bw, oral gavage, OECD 422. Target organ: Kidneys NOAEC: 100 ppm (352 mg/m ³) inhalation, OECD 413. Target organ: decreased body weight (gain), food consumption, food efficiency.	Read across, methacrylic acid (CAS# 79-41-4)	REACH disseminated dossier
Genetic toxicity	Negative		REACH disseminated dossier
Carcinogenicity	Not carcinogenic	Read across, methyl methacrylate (CAS# 80-62-6)	REACH disseminated dossier
Fertility/Development	NOAEL: > 1000 mg/kg bw, oral gavage, OECD 422. NOAEL: >400mg/kg bw, oral gavage, OECD 416. NOAEC: >2028 ppm, inhalation, OECD 414, rat. NOAEL: >450 mg/kg bw, oral gavage, OECD 414, rabbit. NOAEC: >300 ppm (1076 mg/m ³), inhalation, OECD 414, rat	Read across, methyl methacrylate (CAS# 80-62-6) Read across, methyl methacrylate (CAS# 80-62-6) Read across, methyl methacrylate (CAS# 80-62-6) Read across, methyl methacrylate (CAS# 80-62-6)	REACH disseminated dossier

2-Hydroxyethyl methacrylate (CAS# 868-77-9) is registered under REACH. The dossier shows a full data set on toxicity, please refer to Table 5. Reliable data to derive the tolerable daily intake are available.

3.2 Derivation of the Indicative Drinking Water Target Value

Based on the available information an indicative TDI is derived. Depending on the information available, choices are made about assessment factors to be used, following existing guidelines (e.g. REACH guidelines) as much as possible [RIVM 2017]. In this case a full REACH dossier is available.

In table 6 the toxicity data for the selected key study is presented.

Table 6 Summary of toxicity endpoints for 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Endpoint	Test guideline	Result
Sub-acute repeated dose toxicity	OECD 422	NOAEL: 100 mg/kg bw, oral gavage. Target organ: Kidneys

The key NOAEL is 100 mg/kg bw day from an OECD 422 study via the oral route. Based on the data in table 7 the DNEL long term systemic for the general population is derived in the REACH dossier. The results are presented in table 6.

Table 7 Derivation of the DNEL for 2-Hydroxyethyl methacrylate (CAS# 868-77-9)

Parameter	AF*	Comments
Dose response relationship	1	The NOAEL is reliable. No adjustment is required.
Duration of exposure	6	The NOAEL is based on a subacute study of approx. 54 d for the relevant sex (males). AF 6 for extrapolation from sub-acute to chronic represents a conservative approach as this study period exceeds a normal subacute study period.
Interspecies differences	4	Default for allometric scaling.
Interspecies differences, remaining	2.5	Default for remaining uncertainties.
Intraspecies differences	10	Default for intraspecies differences.
Quality of the database	1	The key study is of high quality.
Remaining uncertainties	1	The starting point is a screening study with a somewhat higher level of uncertainty. However, a DNEL analysis of the metabolites and the analogous Hydroxypropyl methacrylate (CAS# 27813-02-1)(on molar base) does not indicate remaining uncertainties.
Overall assessment factor	600	

* Source: ECHA Guidance on Information Requirements and Chemical Safety Assessment

$$\begin{aligned}
 \text{DNEL} &= \text{NOAEL} / \text{AF}_{\text{overall}} \\
 &= 100 / 600 \\
 &= 0.16 \text{ mg/kg-bw/day}
 \end{aligned}$$

The indicative drinking water target value (iDTV) is calculated using equation B as referred to in section 3.7.2 of Technical Guidance 27 [EC, 2018]:

$$\text{iDTV} = 0.2 * \text{DNEL} * \text{bw} / \text{uptakeDW}$$

with

bw = 70 kg [ECHA, 2008]

uptakeDW = 2 liters [ECHA, 2008]

$$\begin{aligned} \text{iDTV} &= 0.2 * 0.16 * 70 / 2 \\ &= 1.67 \end{aligned}$$

4 Organoleptic effects on drinking water

There is no information available regarding adverse organoleptic effects on drinking water. The substance has very low vapor pressure at ambient temperature. This suggests that the presence of 1.67 mg/L in water will not induce significant adverse effects on the organoleptic properties of drinking water prepared from surface water.

5 Discussion

The objective of this report is to derive an indicative Drinking Water Quality Standard for 2-Hydroxyethyl methacrylate (CAS# 868-77-9). A full toxicity data set available to derive a Derived No Effect Level.

The indicative drinking water target value for 2-Hydroxyethyl methacrylate (CAS# 868-77-9) was calculated at 1.67 mg/L based on the REACH DNEL. Organoleptic effects on drinking water are not foreseen due to the low vapor pressure.

6 References

- EC, 2018. "Technical Guidance for Deriving Environmental Quality Standards"; Guidance Document No. 27, updated version 2018.
- ECHA disseminated dossier, <https://www.echa.europa.eu>, CAS# 868-77-9) last consulted 13 February 2023
- ECHA Substance evaluation, Template_SEV_conclusion_and_report (europa.eu) last consulted 24 March 2023
- ECHA Guidance on Information Requirements and Chemical Safety Assessment. Guidance on Information Requirements and Chemical Safety Assessment - ECHA (europa.eu) last consulted 24 March 2023
- Ecotox database, <https://cppub.epa.gov/ecotox>, CAS# 868-77-9) last consulted 13 February 2023
- EU Risk Assessment Report for MMA 2002 RAR-MMA (europa.eu) last consulted 7 March 2023
- Min IenW, 2019. "Handboek immissietoets, versie 2019"; Ministerie van Infrastructuur en Milieu, Rijkswaterstaat; concept document versie oktober 2019.
- OECD SIDS 2001, Microsoft Word - 868779.doc (oecd.org), download 14 February 2023
- R. van Doorn en A.P. van Harreveld; RIVM-report 609200001; June 11, 2009
- RIVM Normen 2-Hydroxyethyl methacrylate | Risico's van stoffen (rivm.nl) last consulted 6 March 2023
- 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.
- Ruijten, 2009. "Assessment of odour announce in chemical emergency management"; M.W.M.M Ruijten.



Appendix

1. Testing

The toxicology of 2-Hydroxyethyl methacrylate (CAS# 868-77-9) has been fully evaluated to support registration according to the REACH regulation. The toxicity findings are quoted below and were retrieved from: [Registration Dossier - ECHA \(europa.eu\)](#) last consulted 13 February 2023

Toxicokinetics

Reliable experimental data exists to demonstrate that 2-Hydroxyethyl methacrylate is rapidly metabolized by a ubiquitous metabolic pathway within the body. 2-Hydroxyethyl methacrylate is metabolised to ethylene glycol and methacrylic acid. There is a high level of confidence based upon experimental data showing that the half-life of 2-Hydroxyethyl methacrylate is in the order of a few minutes. Furthermore, studies in guinea pigs and in mice with 2-Hydroxyethyl methacrylate indicate that most of the administered material is rapidly cleared from the body following metabolism to CO₂.

Methacrylate esters in general

For the understanding of the toxicokinetic of the hydroxyalkyl-methacrylate esters like HEMA (and HPMA) it is important to understand the general metabolism of methacrylate esters in mammals. For MMA and other short-chain alkyl-methacrylate esters extensive toxicokinetic data are available. These data have been reviewed and summarized in the EU Risk Assessment for MMA as well as the OECD SIAR for short-chain alkyl-methacrylate esters.

In brief, after oral or inhalation administration methacrylate esters are expected to be rapidly absorbed and distributed. Dermal absorption of esters is extensive only with occlusion of the site. Toxicokinetics seem to be similar in man and experimental animals. MMA and other short chain alkyl-methacrylate esters are initially hydrolyzed by non-specific carboxylesterases to methacrylic acid and the structurally corresponding alcohol in several tissues. Methacrylic acid (MAA) and the corresponding alcohol are subsequently cleared predominantly via the liver (valine pathway and the TCA (Tricarboxylic Acid) cycle, respectively). The carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body and are known to show high activity within many tissues and organs, including the liver, blood, GI tract, nasal epithelium and skin. Those organs and tissues that play an important role and/or contribute substantially to the primary metabolism of the short-chain, volatile, alkyl-methacrylate esters are the tissues at the primary point of exposure, namely the nasal epithelia and the skin, and systemically, the liver and blood.



Figure: Ester hydrolysis by carboxylesterases, "R" is a placeholder for any alkyl or hydroxyalkyl group

As supporting evidence, metabolism and half-life data from a range of lower alkyl-methacrylate esters indicate that this category of methacrylate esters of comparable molecular weight (HEMA MW 130.1; HPMA MW 144.2) are rapidly hydrolysed by ubiquitous carboxylesterases. First pass (local) hydrolysis of the parent ester has been shown to be significant for all routes of exposure.

Conjugation

The reactivity towards glutathion of more than 50 methacrylates and other chemicals with related structures has been estimated with a QSPR model by Cronin (2012). For both hydroxyalkyl methacrylates it is predicted that they are slightly reactive towards glutathione(GSH). This is consistent with experimental data by Freidig et al. (1999) who investigated and compared the reactivity with glutathion of a series of acrylate and methacrylate esters.

Methacrylate esters can conjugate with GSH in vitro, although they show a low reactivity, since the addition of a nucleophile at the double bond is hindered by the alpha-methyl side-group. Hence, ester hydrolysis is considered to be the major metabolic pathway for alkyl-methacrylate esters, with GSH conjugation only playing a minor role in their metabolism, and then possibly only when very high tissue concentrations are achieved.

HEMA

A non-GLP toxicokinetic study of both HEMA and HPMA in rats via intravenous administration was conducted to evaluate the potential quick hydrolysis of both HEMA and HPMA in vivo (Dow, 2017).

The results showed that HEMA dropped rapidly after administration and were not quantifiable by 60 minutes with limit of quantitation (LOQ) of 45.0 ng/mL. The estimated half-life for HEMA was around one minute (i.e. 0.84 and 1.06 minutes for the two tested animals), indicating that the current study results support the assumption that HEMA was quickly hydrolyzed after intravenous administration in rats.

A comparable conclusion has been made in an earlier study which used a combination of *in vitro* ester hydrolysis experiments with liver microsomes and whole rat blood and a PBPK model, slightly modified from the model developed by Jones (2002) in a study with lower alkyl methacrylates (Dow, 2013). This study was conducted to investigate *in vitro* hydrolysis rates of methacrylate esters for which limited data exist. Seven methacrylate esters, including 2-hydroxyethyl methacrylate (HEMA) were chosen for experimental determination of metabolism rates in whole rat blood and rat liver enzymes at a single substrate concentration. All seven methacrylates were quickly hydrolyzed to methacrylic acid (MAA) and the corresponding alcohol in both whole rat blood and rat liver microsomes. The half-life of HEMA after incubation with rat liver microsomes was 4.62 minutes, in whole rat blood 99 minutes. Based on the *in vivo* hydrolysis rates, the PBPK model predicted the following rates for rat liver: V_{max} = 39 mg/hr/g liver and K_m = 116 mg/L. The corresponding half-lives *in vivo* ($T_{1/2\alpha}$ = 0.040 hr / 2.4 min – distribution and metabolism; $T_{1/2\beta}$ = 0.077 hr / 4.62 min – metabolism phase) are very short and consistent with the *in vivo* data above on rats (Dow 2017) and below on mice (Durner 2009).

Durner et al (2009) measured the absorption, distribution and toxicokinetics of HEMA in mice following oral and subcutaneous injection routes. In this study, uptake, distribution, and excretion of ^{14}C -HEMA applied via gastric tube or subcutaneous administration at dose levels well above those potentially encountered in dental care were examined in mice to test the hypothesis that HEMA can reach cytotoxic levels in mammalian tissues. Each mouse received HEMA (20 mmol/kg bw [104 mg/kg/25 g mouse], dissolved in 0.9% NaCl solution), labeled with a tracer dose of radioactive ^{14}C -HEMA 0.7 kBq/g bw) either by subcutaneous injection beneath the shoulder skin or via gastric tube. The clearance of ^{14}C -HEMA and the ^{14}C content in organs, wall and content of organs, blood, urine, feces and exhaled air were determined by measuring the ^{14}C activity. In a separate experiment, each mouse was kept in a closed chamber with controlled air flow. The exhaled air was captured during the total experimental period by flowing through 7 bottles, one behind the other, filled with 250 ml ice-cold 5 N NaOH. $^{14}\text{CO}_2$ was captured as $^{14}\text{C Na}_2\text{CO}_3$ and the total ^{14}C -activity determined. Urine and feces were collected at 0.5, 1, 2, 6, 12 and 24 h after the beginning of the experiment.

^{14}C -HEMA was taken up rapidly from the stomach and intestines after gastric administration and was widely distributed in the body following administration by each route. After oral application in the first *in vivo* experiment ^{14}C was found to be 62% of the applied ^{14}C -HEMA dose in the entire mouse 5 min after application. Highest ^{14}C contents were found in the content of the stomach and in the wall of stomach (19.8% and 10.5%, respectively) followed by liver (5.1%), blood (3.3%), brain and lung (0.2%). After subcutaneous application in the first *in vivo* experiment ^{14}C was found to be 43% of the applied ^{14}C -HEMA dose in the entire mouse 5 min after application. Highest ^{14}C contents were found in muscle (18.4%) followed by blood (5.7%), skin (5.6%), injection area (3.7%) and liver (2.7%).

Most ^{14}C was excreted within one day as $^{14}\text{CO}_2$. After 24 h the elimination of ^{14}C was nearly complete (0.5% - 1% ^{14}C was found in the entire mouse) by either route of administration. The plasma half-life period of ^{14}C -HEMA was estimated to be lower than 10 min.

After oral application in the second in vivo experiment mice excreted ^{14}C equivalent to 7% of the applied ^{14}C -HEMA dose via urine and to about 23% via feces within 24 h. Mice exhaled ^{14}C as $^{14}\text{CO}_2$ equivalent to about 62% of the applied dose within 24 h. ^{14}C was exhaled as $^{14}\text{CO}_2$ equivalent to 59% of the applied dose even within 1 h by mice. The total ^{14}C recovery increased to 94% by 24 h following oral dosing.

After subcutaneous application in the second in vivo experiment mice excreted ^{14}C equivalent to about 14% of the applied ^{14}C -HEMA dose via urine and to about 12% via feces within 24 h. Mice exhaled ^{14}C as $^{14}\text{CO}_2$ equivalent to about 67% of the injected dose within 24 h. The total ^{14}C recovery increased to 95% up by 24 h.

The authors concluded that the metabolism of HEMA in vivo in mice is so rapid that the concentration of HEMA is only in the nanomolar range, indicating that the toxic levels for mammalian cells [micromolar to millimolar range] will not be reached. It is therefore unlikely that HEMA released from dental materials could have any systemic toxic effects. The study did not support the hypothesis, that HEMA reaches toxic levels in body tissue.

Reichl et al (2002) investigated the metabolism and toxicokinetics of HEMA in guinea pigs using ^{14}C -HEMA labeled on the carboxyl carbon and administered by either oral or subcutaneous routes. Low fecal ^{14}C levels (about 2% of the dose) and urinary levels of about 15% after 24 h were noted with either route of administration. Direct measurement of exhaled radiolabeled CO_2 showed that about 70% of the dose left the body via the lungs. Clearance from most tissues following gastric and intradermal administration was essentially complete within one day. The authors postulated the existence of reactive oxygenated intermediates based on the ratio of radiolabeled pyruvate to malate in bile; however, no direct evidence for these postulated structures was presented.

Primary Metabolites

MAA

For MAA, the common metabolite for these esters, a comparison of measured blood concentration data after i. v. administration of 10 and 20 mg/kg MAA was made and a simulation was performed based on a one-compartment model. This shows good agreement with the measured data in vivo (Jones, 2002).

Based on that information, the following kinetic parameters were determined from a simultaneous fit of the in vivo data to a one-compartment model with non-linear elimination ($V_{ss} = 0.039 \text{ L/SRW}$; $V_{max} = 19.8 \text{ mg/hr} \times \text{SRW}$; $K_m = 20.3 \text{ mg/L}$; SRW: standard rat weight = 250 g) the half-life of MAA in blood was calculated as 1.7 min.

EG

As described in the ATSDR review (2010), "Ethylene glycol is converted to glycolaldehyde by nicotinamide adenine dinucleotide (NAD)-dependent alcohol dehydrogenase. Subsequent reduction of NAD results in the formation of lactic acid from pyruvate. Glycolaldehyde has a brief half-life and is rapidly converted to glycolic acid (and to a lesser extent glyoxal) by aldehyde dehydrogenase and aldehyde oxidase, respectively. Glycolic acid is oxidized to glyoxylic acid by glycolic acid oxidase or lactic dehydrogenase.

Glyoxylic acid can be metabolized to formate, glycine, or malate, all of which may be further broken down to generate respiratory CO_2 , or to oxalic acid, which is excreted in the urine. In excess, oxalic acid can form calcium oxalate crystals. Rate-limiting steps in the metabolism of ethylene glycol include the initial formation of glycolaldehyde and the conversion of glycolic acid to glyoxylic acid, both of which are saturable processes. The conversion of glycolic acid to glyoxylic acid is the most rate-limiting step in ethylene glycol metabolism."

The metabolism of Ethylene glycol, namely the saturation, has a substantial impact on renal and developmental effects in animals and is thus picked up in Repeated Dose Toxicity Toxicity for Reproduction.

Conclusions

Methacrylate esters are readily absorbed by all routes and rapidly hydrolyzed by carboxylesterases to methacrylic acid (MAA) and the respective alcohol, ethylene glycol. Clearance of the parent ester from the body is in the order of minutes. The primary methacrylic metabolite, MAA, is subsequently cleared rapidly from blood and, as indicated by studies with MMA, this metabolism is by standard physiological pathways, with the majority of the administered dose being exhaled as CO₂. The metabolism of EG, the primary glycolic metabolite of HEMA is also well understood as based on standard physiological pathways. CO₂, or oxalic acid, which is excreted in the urine, are the ultimate metabolites. The similarity of metabolism between HEMA and MMA also implies that systemic toxicity data on MMA and other lower chain alkyl methacrylic acid esters are relevant to the potential toxicity profile of HEMA.

Thus, following absorption of MMA or HEMA into the body the metabolic disposition of the two materials are likely to be similar differing substantively only on the alcohol/glycol moiety released and toxicity data for MMA may also be of relevance to HEMA.

Local effects (irritation) resulting from the hydrolysis of the ester to MAA are only observed following inhalation exposure and this has been shown to be due to the localised concentration of non-specific esterases in nasal olfactory tissues. In summarising the available PBPK data on MMA SCOEL concluded that "Extensive PBPK modelling work has predicted that on kinetic grounds for a given level of exposure to MMA human nasal olfactory epithelium will be at least 3 times less sensitive than that of rats to the toxicity of MMA" (SCOEL, 2005). For HEMA, however, similar to EHMA, the lower alkyl methacrylate category member with the highest molecular weight and low vapour pressure, it is unlikely that this is a relevant mode of action, since the vapour pressure is too low so that toxic, local MAA levels cannot be reached in the respective tissues.

Studies indicate that HEMA may react both non-enzymatically and enzymatically with glutathione and that N-acetylcysteine may antagonize the cytotoxicity and genotoxicity of HEMA (and by extension HPMA) in vitro. These effects however occur only at very high, millimolar concentrations and is consistent with the prediction of slight reactivity with GSH based upon QSAR considerations of their structures (Cronin 2012). As weak electrophiles with only transient presence within the body they will be unlikely to contribute significantly, as compared with the primary metabolites, to the profile of systemic toxicity observed after repeated dosing. In this regard, the systemic toxicity of MAA is non-specific and common to both esters, whereas the glycols and their subsequent metabolism are likely responsible for any differences observed in the toxicity profile of the parent ester in vivo. Since the systemic toxicity of EG is more marked than that of PG this is likely responsible for the more marked toxicity observed with HEMA compared with HPMA upon repeated dosing.

Summary and discussion on Toxicokinetics

The read across hypothesis and the satisfaction of the higher tier data requirements for HEMA relies on the observation that HEMA is metabolized very rapidly within the body to their respective alcohol (EG) and methacrylic acid (MAA) and as a consequence repeated dose systemic toxicity reflect the combined toxicities of the primary metabolites, which have already been studied extensively. Toxicokinetics therefore is a key element in the mode of action for many endpoints as well as in the read across hypothesis.

Experimental data exists to demonstrate that HEMA is metabolized by a ubiquitous metabolic pathway for all esters, including methacrylates within the body. HEMA is metabolised to EG and methacrylic acid. There is a high level of confidence based upon experimental data showing that the half-life of HEMA is in the order of a few minutes (Dow, 2017). Supporting evidence for the experimental data on HEMA is coming from data on a number of structurally related methacrylate esters in the same range of molecular weight and polarity (Jones, 2002; Dow, 2013).

Acute oral toxicity (rat)

2-Hydroxyethyl methacrylate was tested in an acute oral toxicity test in rats at concentrations up to 6740 mg/kg according to "Appraisal of the safety of chem by the Staff of the Division of Pharmacology, FDA, 1959 in food, drugs and cosmetics". LD50 for acute oral toxicity was determined to be >5000 mg/kg

Acute dermal toxicity(rat)

The acute dermal toxicity of Hydroxypropyl methacrylate (CAS# 27813-02-1) was tested in a limit test in a concentration of 5000 mg/kg in 6 New Zealand White rabbits. 0/6 animals died. LC50 dermal of Hydroxypropyl methacrylate (CAS# 27813-02-1) is considered to be > 5000 mg/kg.

Mortalities occurred within 24 h. Group Dose 24 h 14 days, I 3.40 g/kg 1/10 1/10, II 4.26 g/kg 1/10 1/10 III 5.35 g/kg 4/10 4/10, IV 6.74 g/kg 8/10 8/10. In the autopsy of the animals that died haemorrhages of the stomach- and colon mucosa were found. At test end no pathological- or anatomical changes were found in the cranium-, chest- and abdominal cavity were found.

Acute inhalation toxicity

No data

Skin/Eye Irritation

The skin irritation potential of 2-Hydroxyethyl methacrylate has been evaluated in a test in rabbits according to "Appraisal of the safety of chemicals in food, drugs and cosmetics by the Staff of the Division of Pharmacology, FDA, 1959 in food, drugs and cosmetics" (Sterner, Stiglic, 1977). Undiluted 2-Hydroxyethyl methacrylate was applied with occlusion to the scarified and non-scarified skin of six rabbits for 24 hr. 2/6 animals had erythema scores of 1 after 24 hrs (one animal died not treatment related within 24 hrs.). After 72 hours none of the remaining five animals showed erythema. 0/6 animals showed oedema after 24 and 72 hrs. 2-Hydroxyethyl methacrylate was found to be not irritating. However the substance has a harmonized classification as irritating to skin.

For eye irritation the key study (Sterner, 1977) was assigned a Klimisch rating of 2, reliable with restriction. The test was performed in rabbits according to the Appraisal of the safety of Chemicals in foods, drugs, and cosmetics by staff of the Division of Pharmacology, FDA acc. to Draize (1959). The study was re-evaluated according to UN-GHS criteria. 6/6 animals had opacity scores ≥ 1 which were reversible within 7 days. The substance is irritating to the eyes.

Skin sensitization

The skin sensitization potential of 2-Hydroxyethyl methacrylate is clearly documented by human and animal data. The key study is summarized below: Guinea pigs exhibited none or slight responses to sensitization with low concentrations of 2-hydroxyethyl methacrylate in the guinea pig maximization test, while 60-100% reacted to high concentrations regardless of the vehicle used for induction. Petrolatum, water, soybean oil and a mixture of oil and 2-butanone (sbomek) were used as vehicles for elicitation. The neat methacrylate was less effective than dilutions in any vehicle, petrolatum being the best. The major determinant of the frequency or response was the concentration used for intradermal induction.

Repeated dose toxicity oral

The key study is summarized; 2-Hydroxyethyl methacrylate was studied for oral toxicity in rats in an OECD 422, combined repeated dose and reproduction/developmental toxicity screening test at doses of 0, 30, 100, 300 and 1000 mg/kg/day. One male and 6 females of the 1000 mg/kg group (12 animals of each sex) died during the treatment period. Male rats in 300 mg/kg and 1000 mg/kg dose groups had elevated kidney weights and elevated levels of urea nitrogen (BUN). Histopathological changes in the kidney of male rats were confined to minimal (+/-) grade severity observations in 1000 mg/kg group animals that included: renal tubule dilatation (3 rats); collecting duct dilatation (2 rats); unilateral cyst (1 rat); diffuse mineralization (1 rat) and neutrophilic cellular infiltration (1 rat).

In addition, basophilic tubules and eosinophilic bodies in proximal tubules were described in similar numbers of animals for both control and 1000 mg/kg groups. The single histological observation in 300 mg/kg group males was focal renal tubule degeneration of minimal (+/-) grade in one male rat. Female rats had elevated kidney weight at 1000 mg/kg and at 100 mg/kg, but not at 300 mg/kg. Histopathological changes in kidney tissue described in one female rat as grade 1 (+) unilateral neutrophilic cellular infiltration into the medulla and papilla were observed in female rats only at the 1000 mg/kg dose level. Clinical chemistry measurements were not reported for female rats. Overall, these results for repeated dose toxicity testing of 2-Hydroxyethyl methacrylate indicate that the kidney is a target organ for toxicity in both male and female rats. Male rats had elevated kidney weights and BUN levels at 300 and 1000 mg/kg dose levels. However, histopathology was described as minimal and occurred only in a few animals. The 100 mg/kg dose was the No Observed Adverse Effect Level (NOAEL) for these effects on kidney in males. Female animals had elevated kidney weights and histopathological changes in one animal and only at the 1000 mg/kg dose level; 300 mg/kg was the NOAEL for lethality and effects on kidney in females.

Repeated dose toxicity by inhalation

They key study is summarized; In a valid guideline study acc. to OECD 413 (Sub-chronic inhalation toxicity: 90-day exposure of rats), methacrylic acid induced signs of general toxicity as indicated by decreased body weight, body weight gain, food consumption and transiently food efficiency in the high concentration male animals. At a concentration as high as 350 ppm (1232 mg/m³), the local irritating effect was marginal, indicated by the hypertrophy/hyperplasia of the respiratory epithelium in the nasal cavity of two female animals. Substance-related changes of the sexual organs were not noted in any of the exposed animals, nor were there any changes of sperm mobility and sperm head counts. Under the current test conditions, the no-observed adverse effect level (NOAEL) for both, local and systemic effects, in this study is 100 ppm (352 mg/m³) for male and female rats.

Repeated dose toxicity by dermal exposure

No references found to this type of study.

Genetic toxicity in vitro

In a reverse gene mutation assay in bacteria (Ames test), strains TA1535, TA1537, TA98, TA100 of *Salmonella typhimurium*, and *E. coli* WP2 uvr A were exposed to 2-hydroxyethyl methacrylate (97.6 %) at concentrations of 0, 313, 625, 1250, 2500 and 5000 µg/plate in the presence and absence of mammalian metabolic activation S9-mix. In two independent experiments 2-Hydroxyethyl methacrylate was investigated for its potential to induce gene mutations according to the preincubation test. No toxic effects occurred in the test groups with and without metabolic activation in both independent experiments. 2-Hydroxyethyl methacrylate did not induce mutations in the *Salmonella typhimurium* strains TA98, TA100, TA1535, TA 1537 and *E. coli* uvr A. Appropriate reference mutagens were used as positive controls. The positive controls induced the appropriate responses in the corresponding strains. There was no evidence of induced mutant colonies over background. 2-Hydroxypropyl methacrylate was not mutagenic to *Salmonella typhimurium* TA100, TA98, TA1535, TA1537 and *Escherichia coli* WP2 uvrA, with or without an exogenous metabolic activation system.

2-Hydroxyethyl methacrylate has been evaluated for its ability to induce chromosomal aberrations in mammalian cells in culture (MHW 1997). Kusakabe et al. (2002) evaluated the clastogenic potential of 2-Hydroxyethyl methacrylate along with many other substances in Chinese hamster lung cells in culture, exposed to concentrations up to 1.3 mg/ml. 2-Hydroxyethyl methacrylate was reported to induce structural chromosome aberrations following 6-hour exposure of cells but only in the presence of S9 at 1.3 mg/ml. Continuous exposure of cells for 24 or 48 hours without S9 also caused an elevated incidence of chromosome aberrations (from 0.16 mg/ml for the 48-hour exposure and from 0.65 mg/ml for the 24-hour exposure). Polyploidy was reported after both short-term treatment and 48-hour continuous treatment exposures. However, no dose-dependency was observed for polyploidy in the short-term treatment with metabolic activation. These effects were found at exposure levels without cytotoxicity or at concentrations which caused <50% cell death (no toxicity up to 0.65 mg/ml).

For careful interpretation of these results two publications by Fujita et al (2016) should be considered. If the cytotoxicity index relative cell count (RCC) is replaced with a new index, RICC or RPD (relative increase in cell count/relative population doubling), the result was identified as being possibly false positive.

Hydroxypropyl methacrylate (2-methyl-2-propenoic acid monoester with 1,2- propanediol) was evaluated in the in vitro Chinese hamster ovary cell/hypoxanthineguanine- phosphoribosyl transferase (CHO/HGPRT) forward gene mutation assay. The genotoxic potential of the test material was assessed in the absence and presence of an externally supplied metabolic activation (S9) system. The concentrations ranged from 45.1 to 1442 µg/ml in the absence and presence of S9. The highest concentration was based on the assay system limit of 10 mM. The adequacy of the experimental conditions for detection of induced mutation was confirmed by employing positive control chemicals, ethyl methanesulfonate for assay in the absence of S9 and 20- methylcholanthrene for assay in the presence of S9. Solvent control cultures were treated with the solvent used to dissolve the test material (i.e. distilled water). The results of the in vitro CHO/HGPRT forward gene mutation assay with hydroxypropyl methacrylate indicate that under the conditions of this study, the test article was non-mutagenic when evaluated in the absence or presence of an externally supplied metabolic activation (S9) system.

2-Hydroxypropyl methacrylate induced structural chromosomal aberrations in CHL/IU cells with and without an exogenous metabolic activation system. Polyploidy was induced without an exogenous metabolic activation system.

Genetic toxicity in vivo

A bone marrow micronucleus study (OECD474) in seven-week-old, Sprague Dawley rats was conducted to assess the mutagenic potential of 2-Hydroxyethyl methacrylate. The test substance was administered twice at 24 -hour interval by oral gavage at three doses of 500, 1000 and 2000 mg/kg to groups of 5 male rats. Twenty-four hours after the final administration bone marrow samples were prepared and were examined for incidence of micronucleated polychromatic erythrocytes. The test substance did not induce significant increases in the micronucleated polychromatic erythrocytes in any treated groups.

Cyclophosphamide, used as positive treatment, did cause an increase in micronucleated PCEs.

Carcinogenicity

No chronic exposure toxicity data are available for 2-Hydroxyethyl methacrylate. However, there is ample information to indicate that 2-hydroxyethyl methacrylate has a low potential to be carcinogenic and that studies may be waived. Data are available for potential genotoxicity of 2-hydroxyethyl methacrylate.

Additionally, information is available on the carcinogenic potential of methyl methacrylate, a close structural analogue of 2-hydroxyethyl methacrylate. It is concluded that carcinogenicity studies of 2- hydroxyethyl methacrylate are not necessary and may be waived because:

2-hydroxyethyl methacrylate was not found to be genotoxic in a battery of tests in vitro and in vivo.

Read-Across to methyl methacrylate (CAS# 80-62-6) Data. methyl methacrylate (CAS# 80-62-6), a close structural analogue of 2-hydroxyethyl methacrylate, has been evaluated in chronic toxicity/carcinogenicity tests in mice and rats and found not to be a carcinogen.

2-hydroxyethyl methacrylate has been evaluated for genotoxic potential in bacterial cells in culture and were found not to be mutagenic in this assay system. Further, 2-hydroxyethyl methacrylate was found not to be mutagenic in mammalian cells in culture [CHL V79 cell assay], albeit 2-hydroxyethyl methacrylate was evaluated only in the absence of S-9. 2-hydroxyethyl methacrylate was reported to cause chromosomal aberrations in mammalian cells in culture, but an in vivo micronucleus study with 2- hydroxyethyl methacrylate indicated that this material was not clastogenic in vivo. These results are in accord with genotoxicity assay findings for methyl methacrylate. methyl methacrylate was not active in bacteria mutation assays but did cause chromosomal aberrations in mammalian cells in culture, an effect not observed in vivo. On balance, 2-hydroxyethyl methacrylate is not a genotoxic material.

Methyl methacrylate (CAS# 80-62-6) as a member of the chemical class of short-chain alkyl esters of methacrylic acid has been evaluated for carcinogenic potential in long-term toxicity studies in mice and rats. There is no indication of a potential for carcinogenicity.

NTP (1986) conducted a carcinogenicity study that showed no treatment-related tumours in male and female F344/N rats and male and female B6C3F1 mice following inhalation exposure to 500 or 1000 ppm for 102 weeks (6 h/d, 5 d/wk).

Groups of 50 male F344/N rats were exposed to methyl methacrylate (purity >99%; containing 0.04 mg/1 equivalent to 10 ppm monomethyl ethyl ether of hydroquinone as an inhibitor of polymerization) by inhalation at ca. 0, 2.05 and 4.1 mg/L (equivalent to 500 or 1000 ppm), female F344/N rats at ca. 0, 1.03 or 2.05 mg/L (equivalent to 250 or 500 ppm) and male and female B6C3F1 mice at ca. 2.05 or 4.1 mg/L (equivalent to 500 or 1000 ppm), 6 hours a day, 5 days a week for 102 weeks (NTP, 1986).

No significant differences of the survival rates were observed between any groups of rats and mice. Reductions in mean body weights of high dosed animals were considered as secondary effects based on the observed inflammations and degenerations of the olfactory epithelium in all methyl methacrylate (CAS# 80-62-6) treatments. The marginal increase in the incidence of mononuclear-cell leukaemia observed in female rats (control 11/50; low-dose 13/50; high-dose 20/50) fell within the range of values seen in historical controls. Both in mice and rats no treatment-related tumours were observed.

The EU Risk Assessment Report for methyl methacrylate (CAS# 80-62-6) (2002) concluded that: There is no relevant concern on carcinogenicity in humans and animals.

Epidemiology data on increased tumour rates in exposed cohorts were of limited reliability and cannot be related to methyl methacrylate (CAS# 80-62-6) as the solely causal agent. Therefore there are no reasons to assume that methyl methacrylate (CAS# 80-62-6) should be carcinogenic in humans.

Reproductive and developmental toxicity

The available OECD 422 screening studies with 2-hydroxyethyl methacrylate (and Hydroxypropyl methacrylate (CAS# 27813-02-1) do not show any indication of reproductive/developmental effects up to 1000 mg/kg/d, i.e. above the threshold of systemic toxicity.

For ethylene glycol (EG), the alcohol metabolite of 2-hydroxyethyl methacrylate, the observed developmental effects must be considered in the light of possible relevance to humans. Relevant studies are then predominantly limited to those employing continuous dosage (e.g., feeding) and/or those species without dependence on the inverted yolk sac placenta during ontogenesis (excluding rodent species mouse and rat). In these relevant studies either no developmental effects were observed, or where they were observed only at maternally toxic doses. Hence, although some concern exists for reproductive effects of 2-hydroxyethyl methacrylate (triggered by the more toxic metabolite EG) there is moderate confidence that these effects would not be expressed in a study with 2-hydroxyethyl methacrylate, as doses would be limited by the systemic toxicity of 2-hydroxyethyl methacrylate.

In summary, it can be concluded with high confidence that 2-hydroxyethyl methacrylate is not a specific developmental toxicant based upon an absence of effects in the 2-hydroxyethyl methacrylate screening study, in the primary metabolite methacrylic acid (and methyl methacrylate (CAS# 80-62-6)) in a relevant dose range in studies with rodent and non-rodent and in the alcohol metabolite EG in rabbits, but also in rodents if exposure schemes are considered which resemble the workplace conditions more closely (continuous dosing). The read-across to the metabolite data is justified by the short half-life of 2-hydroxyethyl methacrylate and the fact that the metabolites – in summary – possess the same modes of action.

From a read across perspective, there is high confidence that data generated on 2-hydroxyethyl methacrylate would act as a conservative surrogate for Hydroxypropyl methacrylate (CAS# 27813-02-1). In summary, with reliable read-across studies for all endpoints in all relevant species the dataset for 2-hydroxyethyl methacrylate is complete.

A study was performed according to OECD TG 416 in compliance with GLP. Methyl Methacrylate was administered to groups of 25 male and 25 female healthy young Wistar rats (P0 parental generation) as an aqueous preparation by stomach tube at dosages of 0; 50; 150 and 400 mg/kg body weight/day. At least 73 days after the beginning of treatment, P0 animals were mated to produce a litter (F1). Mating pairs were from the same dose group and F1 animals selected for breeding were continued in the same dose group as their parents. Groups of 25 males and 25 females, selected from F1 pups to become F1 parental generation (= P1 in the current IUCLID nomenclature), were treated with the test substance at dosages of 0; 50; 150 and 400 mg/kg body weight/day post weaning, and the breeding program was repeated to produce F2 litter. The study was terminated with the terminal sacrifice of the F2 weanlings and F1 adult animals.

Control parental animals were dosed daily with the vehicle (1% Carboxymethylcellulose suspension in drinking water and four drops Cremophor EL and one drop hydrochloric acid).

The mid- and high-dose P0 and F1 parental animals (400 mg/kg bw/d) showed clinical signs of systemic toxicity. The only relevant clinical observation was temporary salivation during a short period after dosing, which is test substance induced. From the temporary, short appearance immediately after dosing it is likely, that this finding was induced by a bad taste of the test substance or local affection of the upper digestive tract. It is, however, not considered to be an adverse toxicologically relevant finding.

In the mid- and high-dose (150 and 400 mg/kg bw/d) P0 generation animals, dose-related intermittent reductions of food consumption were noted, either during premating, gestation, and lactation phases of this study. Less significant changes were noted for the F1 parental animals where the effects were limited to the high-dose group.

High dose F1 parental males had statistically significant lower body weights during several study segments, which led to a statistically significant reduction of the mean terminal body weight resulting in secondary weight changes of brain.

High dose F1 parental females had statistically significant lower body weights during the first weeks after weaning. This weight decrease during major phases of sexual maturation led to an apparent marginal delay of vaginal patency. This minor delay did, however, not result in any corroborative pathological findings nor did it adversely effect F1 female cyclicity, fertility and reproduction. Thus, an influence of the test substance on female sexual maturation is not assumed.

Pathological examinations revealed no test-substance-related changes in organ weights, gross lesions, changes in differential ovarian follicle counts or microscopic findings, apart from an increase in kidney and liver weights in male and female animals in both generations which is presumably related to the treatment. There was no histopathologic lesion observed, that could explain the weight increase. It is regarded to be an adaptive change, most likely caused by an increase in metabolic activity in the two organs, which does not lead to histopathologic findings. It is not regarded to be an adverse effect.

There were no indications from clinical examinations as well as gross and histopathology, that the administration of methyl methacrylate via the diet adversely affected the fertility or reproductive performance of the P0 or F1 parental animals up to and including a dose of 400 mg/kg bw/day. Oestrous cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights and gross and histopathological findings of these organs (including differential ovarian follicle counts in the F1 females) were comparable between the rats of all test groups and ranged within the historical control data of the test facility.

All data recorded during gestation and lactation in terms of embryo-/foetal and pup development gave no indications for any developmental toxicity in the F1 and F2 offspring up to a dose level of 400 mg/kg bw/day. Up to this dose level, the test substance did not adversely influence pup viability and pup body weights. Sex ratio and sexual maturation was not directly affected at any dose level, inclusive the high- dose group (400 mg/kg bw/day).

In a developmental toxicity study on rats acc. OECD 414 by inhalation pregnant CRI: CD Br rats were exposed to methyl methacrylate at concentrations of 0 (control), 99, 304, 1178 and 2028 ppm on days 6- 15 of gestation.

A maternal no observed level was not demonstrated since losses in maternal body weight or decreases in maternal body weight gain and decreases in maternal feed consumption were noted at all exposure levels tested. No embryo or foetal toxicity was evident and no increase in the incidence of malformations or variations was noted at exposure levels up to the highest dose of 2028 ppm. Therefore toxicity to the conceptus was not evident even at exposure levels that resulted in overt maternal toxicity.

In a developmental toxicity study on rabbits acc. OECD 414 methyl methacrylate was tested for its prenatal developmental toxicity in Himalayan rabbits. The test substance was administered as an aqueous preparation to 25 inseminated female Himalayan rabbits by stomach tube at doses of 50; 150 and 450 mg/kg body weight/day on gestation days (GD) 6 through GD 28. The control group, consisting of 25 females, was dosed with the vehicle (1% Carboxymethylcellulose CB 30.000 in drinking water and a few drops Cremophor EL and one drop hydrochloric acid [1% CMC]) in parallel. A standard dose volume of 10 mL/kg body weight was used for each test group. At terminal sacrifice on GD 29, 24-25 females per group had implantation sites.

The following test substance-related adverse effects/findings were noted:

Test group 3 (450 mg/kg body weight/day): Reduced food consumption (-18%) and body weight gain (- 31%), no test substance-related adverse effects on gestational parameters or foetuses

Test group 2 (150 mg/kg body weight/day): reduced food consumption (-13%) and body weight gain (- 27%), no test substance-related adverse effects on gestational parameters or foetuses

Test group 1 (50 mg/kg body weight/day): no test substance-related adverse effects on does, gestational parameters or foetuses.

In conclusion, the no observed adverse effect level (NOAEL) for maternal toxicity is 450 mg/kg bw/d at nominal concentration corresponding to an actual concentration of 406 mg/kg bw/d, the highest dose tested. The no observed effect level (NOEL) for maternal toxicity is nominal 50 mg/kg bw/d (effective 41 mg/kg bw/d) based on effects on food consumption being a consequence of reduced appetite observed at the LOEL (Lowest Observed Effect Level) of 150 mg/kg bw/d (actual 132 mg/kg bw/d).

The no observed adverse effect level (NOAEL) for prenatal developmental toxicity is nominal 450 mg/kg bw/d (actual 406 mg/kg bw/d). No adverse foetal findings of toxicological relevance were evident at any dose in this study.

In an OECD 414 prenatal developmental toxicity study using whole body inhalation methacrylic acid at test concentrations of 50, 100, 200 and 300 ppm, corresponding to 179, 358, 716 and 1076 mg/m³ methacrylic acid did not produce any embryo - or foetal lethality, nor foetal malformations, despite overt maternal toxicity (decreased body weight and feed consumption). The NOEC (teratogenicity) was 300 ppm (1076 mg/m³ or 312 mg/kg bw/day).

The toxicity findings are quoted below and were retrieved from: ECHA Substance evaluation, [Template SEV conclusion and report \(europa.eu\)](#) last consulted 24 March 2023

Respiratory Sensitisation

Some animal and non-animal test methods for the identification of respiratory sensitizers have been described in the literature, but these are not widely accepted yet, nor close to the point where they could enter into a formal validation. Therefore, it is difficult to identify the substance with such a property based on experimental and modelling data. In 2014, following a request by FR-MSCA, the RIVM has run different SAR models (Derek, Jarvis, CatSAR, Enoch, MultiCase) with acrylates, including HEMA. No prediction could be obtained from Derek, CatSAR and Multicase. Enoch gave positive results for respiratory sensitization, whereas HEMA is negative according to Jarvis. According to the RIVM, Derek gives the most reliable prediction of a substance being a respiratory sensitizer and MultiCase the most reliable prediction for respiratory non-sensitization.

Therefore, since no prediction can be obtained with these two models, no conclusion can be reached for the potential respiratory sensitization properties of HEMA based on SAR models. Methacrylates are known to cause respiratory hypersensitivity and asthma, but the mechanism mediating these effects is not known and IgE-mediated reactions from methacrylates have not been reported. Several cases of respiratory sensitization from methacrylates were reported in the literature; among them, two publications in which HEMA was cited are described below. Lindström et al. (2002) reports the case of a female dentist working in general dentistry for 22 years who developed occupational dermatitis and had eye and respiratory symptoms. These symptoms were found to be work-related since they disappeared during weekends and holidays. Inhalation challenge tests were performed in a 6 m³ chamber with a primer and adhesive both containing HEMA. The adhesive and primer induced cough, rhino conjunctivitis and decrease in FEV₁ (forced expiratory volume in one second). Patch test was positive with 1% HEMA and induced itching, swelling and soreness of the eyelids. Therefore, it can be considered as a clear sensitizing reaction to HEMA. Sauni et al. (2008) reports two cases of occupational asthma caused by sculptured nails containing methacrylates. HEMA was detected in the bonding agent, the sealing resin, the sculpture resin and the gel nails. Bronchial provocation tests were performed in an 8 m³ chamber with their own products (they attached the plastic nail with a glue and then filed and sculptured the nails). A dual asthmatic reaction was noted. In the French national network for the monitoring and prevention of occupational diseases (RNV3P) collects every year more than 8000 new occupational health reports throughout France. The French RNV3P network is composed of the 30 Occupational disease consultation centres (CCPP) in mainland France and a number of occupational health services (SSTs) associated with the network. The goal of this network is to record the data from consultations in a national database (patient demographics data, diseases, exposures, job sectors and professions). From this database, several cases of asthma were reported with acrylates or methacrylates but none has been specifically related to HEMA. These cases were mainly observed in dental professionals and nail technicians.

Although HEMA was only cited in few cases of occupational asthma, several human cases were reported with methacrylates compounds (no clear identification of the causal substance), which are an important aetiological factor in this disease.

In particular, based on human data, methyl methacrylate has just been classified in October 2020 by the RAC as Resp. Sens. A C&L proposal would be initiated to classify HEMA as Resp. Sens. Cat. 1, H334 according to CLP Regulation

Bijlage C3 Afleiding indicatieve drinkwatertoetswaarde methacrylzuur: iDWN Methacrylic acid (CAS#79-41-4) FINAL

REPORT

Derivatoin of the indicative Drinking Water Target Value for Methacrylic acid (CAS# 79-41-4)

Client: Sitech Services B.V.

Reference: BJ1982I&BRP002F01

Status: Final/01

Date: 22 May 2024

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Executive Summary

Royal HaskoningDHV was asked by Sitech IAZI bv to derive substance specific water quality standards for Methacrylic acid (CAS# 79-41-4) using the guidance documents. The substance is potentially a degradation product of 2-Hydroxyethyl methacrylate (HEMA), which is used as additive in the production of HDPE.

There is information available about adverse effects Methacrylic acid (CAS# 79-41-4), the drinking water target value is derived. The proposed value for the drinking water target value is set at 3.15 mg/L.

Sitech IAZI bv requests the Wetenschappelijke Klankbordgroep normstelling water en lucht to evaluate and approve the proposed indicative value for water quality standards as summarized in below table.

Table 1 Proposed indicative drinking water target value

Parameter	Proposed Indicative Drinking Water Target Value in mg/L
Methacrylic acid (CAS# 79-41-4)	3.15

1 Introduction

1.1 Preamble

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.

Present wastewater discharge permit holds an obligation to assess the potential risk of the discharge of Methacrylic acid (CAS# 79-41-4) regarding the downstream withdrawal of surface water of the river Meuse for the preparation of drinking water.

The potential impact of the discharge of Methacrylic acid (CAS# 79-41-4) containing 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 regarding aquatic ecosystems and the drinking water preparation functions are relevant.

Royal HaskoningDHV was asked by Sitech to derive a substance specific drinking water target value for Methacrylic acid (CAS# 79-41-4) using the formal guidance document [RIVM, 2017]. This report describes results of literature research and proposes values for water quality standards for this substance.

1.2 Methodology and data mining

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 [EC, 2018]. This guidance is used to derive the drinking water target value for Methacrylic acid (CAS# 79-41-4).

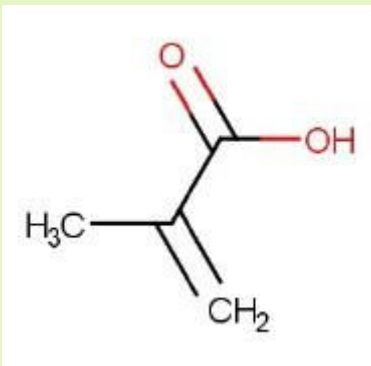
Data of existing evaluations were used as a starting point. As there is no acceptable daily intake (ADI) or tolerable daily intake (TDI) for Methacrylic acid (CAS# 79-41-4) derived by a recognized agency, Royal HaskoningDHV executed an online literature search to compile a dataset with relevant physico-chemical properties and toxicological endpoints, using CAS# 79-41-4. Reviewed sources are:

- RIVM, [Normen | Risico's van stoffen \(rivm.nl\)](https://normen.rivm.nl/)
- ECHA database, [Startpagina - ECHA \(europa.eu\)](https://echa.europa.eu/)
- US-EPA Ecotox database, [Ecotoxicology Database | US EPA](https://ecotox.epa.gov/)
- US-EPA IRIS ([Integrated Risk Information System | US EPA](https://iris.epa.gov/))
- EPA PRTV ([Provisional Peer-Reviewed Toxicity Values \(PPRTVs\) | US EPA](https://www.epa.gov/prrtv/))
- EPA Comptox ([CompTox Chemicals Dashboard \(epa.gov\)](https://comptox.epa.gov/))
- EPA Regional screening levels ([Regional Screening Levels \(RSLs\) | US EPA](https://www.epa.gov/regionalecology/regional-screening-levels-rsls))
- [EFSA | Science, safe food, sustainability \(europa.eu\)](https://efsa.europa.eu/)
- WHO drinking water guidelines (WHO) [Guidelines for drinking-water quality: fourth edition incorporating the first and second addenda \(who.int\)](https://www.who.int/publications-detail/WHO-Guidelines-for-drinking-water-quality-fourth-edition)
- [PubChem \(nih.gov\)](https://pubchem.ncbi.nlm.nih.gov/)
- Generic search on the internet in public literature
- Reports provided by the supplier of the chemical

2 Properties of Methacrylic acid (CAS# 79-41-4)

Table 2 Overview of identifiers for Methacrylic acid (CAS# 79-41-4)

Parameter	Value
Substance name	Methacrylic acid
IUPAC name	Methacrylic acid
Synonyms	2-Methacrylic acid
CAS number	79-41-4
EINECS number	201-204-4
Chemical group according to EPIwin	Neutral organics acid
Cramer class ^{1,2}	III
Harmonized classification	<p>Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation), Index No. 607 -088 -00 -5:</p> <p>Acute Tox 4, H302 Acute Tox 4, H312 Skin Corr. 1A, H314 STOT SE H335</p> <p>Information is available which require stronger hazard classification of an already considered endpoint (acute dermal toxicity, Category 3, H311 instead of Category 4, H312) or hazard classifications for additional endpoints like acute inhalation toxicity (Acute inhalation tox Category 4, H332) and for eye irritation (Eye Dam Category 1, H318).</p>
Substance of very high concern	No
Molecule formula	C ₄ H ₆ O ₂
Smiles	<chem>CC(=C)C(O)=O</chem>

Parameter	Value
Molecule structure	

Class I Structures and related data suggest a low order of oral toxicity. If combined with low human exposure, require a low priority for investigation

Class II Less clearly innocuous than Class I, but no firm indication of toxicity or the lack thereof

Class III Structure and related data permit no initial presumptions of safety or may suggest significant toxicity. These substances deserve the highest priority for investigation.

² 1. G.M. Cramer and R.A. Ford Estimation of toxic hazard - a decision tree approach. Food and Cosmetics Toxicology, Volume 16, Issue 6, December 1978, Page 255-276.

G. Patlewicz, N. Jeliaskova, R.J. Safford, A.P. Worth, B. Aleksiev. An evaluation of implementation of the Cramer classification scheme in the Toxtree software. SAR and QSAR in Environmental Research. Vol. 19, Nos. 5-6, July-September 2008, Page 495-524.

C. Munro, R.A. Ford, E. Kennepohl, J.G. Sprenger. Correlation of Structural class with no-observed-effect levels: proposal for establishing a threshold of concern. Food and Chemical Technology 34 (1996), Page 829-867.

2.1 Physico-chemical properties

Table 3 shows an overview of physico-chemical properties for Methacrylic acid (CAS# 79-41-4).

Table 3 Physico-chemical properties of Methacrylic acid (CAS# 79-41-4)

Property	Value	Additional information	Reference
Molecular weight (g/mol)	86.09		
Melting point (°C)	15.4-15.5	1013 hPa	REACH disseminated dossier
Boiling point (°C)	162	1013 hPa	REACH disseminated dossier
Vapor pressure (hPa)	0.97 hPa	20°C	REACH disseminated dossier
Water solubility (g/L)	98	20°C	REACH disseminated dossier
Henry-coëfficiënt (Pa m ³ /mol)	0.039	25 °C	REACH disseminated dossier

Property	Value	Additional information	Reference
pKa	4.66		REACH disseminated dossier

2.2 Toxicokinetics

Based on the information in the REACH disseminated dossier the substance is expected to be readily absorbed via inhalation, oral and dermal exposure. Rapid clearance from blood and the major excretion route is by exhalation as CO₂. The metabolic route is the standard physiological pathway of Valine catabolism, after reaction with CoA. Local effects may be observed at the site of contact, Due to the corrosive properties of Methacrylic acid local effects are expected at the site of contact." [REACH disseminated dossier].

2.3 Environmental fate

Methacrylic acid is readily biodegradable in water, methacrylic acid is almost completely dissociated at neutral pH, based on a pKa of 4.66, Based on a log Kow of 0.92, bioaccumulation of methacrylic acid is not expected. Due to the low log Koc (average 1.18) and high-water solubility, adsorption to soil is unlikely.

The EU ESR on methacrylic acid concluded: "Due to the fast atmospheric photooxidation and the low resulting concentrations in air, adverse effects on organisms and abiotic effects upon the atmosphere, like global warming and ozone depletion are not expected from methacrylic acid (conclusion (ii))." [REACH disseminated dossier].

Table 4 Environmental fate of Methacrylic acid (CAS# 79-41-4)

Property	Value	Additional information	Reference
Biodegradability	Readily biodegradable	86%, 28 d OECD 301D	REACH disseminated dossier
DT50 hydrolysis	Stable, no half-life calculated	pH = 3,7,11 @ 25 °C, 28d	REACH disseminated dossier
DT50 water/sediment	No data		
Log Koc (L/kg)	1.18 (0.23-1.72)	Low adsorption	REACH disseminated dossier
Log Kow	0.93 @ 22 °C	No bioaccumulation expected	REACH disseminated dossier

2.4 Use

Methacrylic acid (CAS# 79-41-4) is potentially a degradation product of 2-Hydroxyethyl methacrylate (HEMA), which is used as additive in the production of HDPE.

3 Derivation of an indicative drinking water target value

3.1 Overview of available toxicity data for Methacrylic acid

The derivation of the drinking water target value starts with the assessment of the acceptable daily intake following the technical guidance [RIVM, 2017]. The latter parameter is subsequently converted into the drinking water target value based on standard values for body weight and daily drinking water consumption.

Methacrylic acid (CAS# 79-41-4) is registered under REACH at ECHA. The dossier shows a full data set on toxicity, please refer to Table 5. Reliable data to derive the tolerable daily intake are available based on the REACH data.

Table 5 Summary of toxicity endpoints for Methacrylic acid (CAS# 79-41-4)

Property	Value	Additional information	Reference
Acute oral toxicity	1320 mg/kg bw, rat.		REACH disseminated dossier
Acute dermal toxicity	500-1000 mg/kg bw, rat.		REACH disseminated dossier
Acute inhalation toxicity	7.1 mg/L	4h vapour aerosol mixture	REACH disseminated dossier
Skin irritation	Corrosive		REACH disseminated dossier
Eye irritation	Corrosive		REACH disseminated dossier
Sensitisation	Not sensitising		REACH disseminated dossier
Respiratory sensitisation	Respiratory sensitiser suspected	Under investigation	ECHA assessment regulatory needs (ARN)

Property	Value	Additional information	Reference
Repeated dose toxicity	NOAEC: 100 ppm local and systemic effects. OECD 413, rat. NOAEL: >90.3 mg/kg bw/d males, >193.8 mg/kg bw/d females (2000 ppm), 2-year drinking water study, rat.	Pre-guideline, 1964	REACH disseminated dossier
Genetic toxicity	Negative	Conclusion in the REACH dossier. In vivo OECD 489 requested by ECHA.	REACH disseminated dossier
Carcinogenicity	Not carcinogenic NOAEC: 25 ppm local effects. OECD 413, rat.		REACH disseminated dossier
Fertility/Development	NOAEL: >400mg/kg bw, oral gavage, OECD 416, rat.	Read across, methyl methacrylate (CAS# 80-62-6)	REACH disseminated dossier
	NOAEL: >450 mg/kg bw, oral gavage, OECD 414, rabbit.	Read across, methyl methacrylate (CAS# 80-62-6)	
	NOAEC: >300 ppm (1076 mg/m ³), inhalation, OECD 414, rat.		

3.2 Derivation of the Drinking Water Target Value

Based on the available information, an indicative TDI is derived. Depending on the information available, choices are made about assessment factors to be used, following existing guidelines (e.g., REACH guidelines) as much as possible [RIVM 2017]. In this case a full REACH dossier is available.

In Table 6 the toxicity data for the selected key study is presented.

Table 6 Summary of toxicity endpoints for Methacrylic acid (CAS# 79-41-4)

Endpoint	Test guideline	Result
Repeated dose toxicity	2-year drinking water study	NOAEL: >90.3 mg/kg bw/d.

They key NOAEL is >90.3 mg/kg bw day from a 2-year drinking water study. Based on the data in Table 5 the DNEL long term systemic for the general population is derived. The results are presented in table 7.

Table 7 Derivation of the DNEL for Methacrylic acid (CAS# 79-41-4)

Parameter	AF*	Comments
Dose response relationship	1	The NOAEL is reliable. No adjustment is required.
Duration of exposure	2	Chronic study
Interspecies differences	4	Default for allometric scaling.
Interspecies differences, remaining	2.5	Default for remaining uncertainties.
Intraspecies differences	10	Default for intraspecies differences.
Quality of the database	1	The key study is of high quality, there is a large data base.
Remaining uncertainties	1	
Overall assessment factor	200	

* Source: ECHA Guidance on Information Requirements and Chemical Safety Assessment

$$\begin{aligned}
 \text{DNEL} &= \text{NOAEL} / \text{A}_{\text{Overall}} \\
 &= 90.3 / 200 \\
 &= 0.45 \text{ mg/kg bw/day}
 \end{aligned}$$

The indicative drinking water target value (iDTV) is calculated using equation B as referred to in section 3.7.2 of Technical Guidance 27 [EC, 2018]:

$$\text{iDTV} = 0.2 * \text{DNEL} * \text{bw} / \text{uptake}_{\text{DW}}$$

with

bw = 70 kg [ECHA, 2008]

uptake_{DW} = 2 liters [ECHA, 2008]

$$\begin{aligned}
 \text{iDTV} &= 0.2 * 0.45 * 70 / 2 \\
 &= 3.15 \text{ mg/L}
 \end{aligned}$$

4 Organoleptic effects on drinking water

There is no information available regarding adverse organoleptic effects on drinking water. The odor threshold is 10 ppm (REACH disseminated dossier). The substance has high vapor pressure at ambient temperature. No further data is available.

5 Discussion

The objective of this report is to derive an indicative Drinking Water Quality Standard for Methacrylic acid (CAS# 79-41-4). A full toxicity data set available to derive a REACH Derived No Effect Level. The indicative drinking water target value for Methacrylic acid (CAS# 79-41-4) was calculated at 3.15 mg/L based on the REACH data.

6 References

- EC, 2018. "Technical Guidance for Deriving Environmental Quality Standards"; Guidance Document No. 27, updated version 2018.
- REACH disseminated dossier database, <https://www.echa.europa.eu> , [CAS# 79-41-4](#)), last consulted 03-04-2023
- ECHA ARN [Lijst beoordeling regelgevingsbehoeften - ECHA \(europa.eu\)](#), last consulted 03-04-2023
- ECHA Guidance on Information Requirements and Chemical Safety Assessment. [Guidance on Information Requirements and Chemical Safety Assessment - ECHA \(europa.eu\)](#) last consulted 24 March 2023
- Ecotox database, [ECOTOX | Search \(epa.gov\)](#), [CAS# 79-41-4](#)), last consulted 03-04-2023
- EU Risk Assessment Report for MMA 2002 [RAR-MMA \(europa.eu\)](#) last consulted 7 March 2023
- Min IenW, 2019. "Handboek immissietoets, versie 2019"; Ministerie van Infrastructuur en Milieu, Rijkswaterstaat; concept document version October 2019.
- R. van Doorn en A.P. van Harreveld; RIVM-report 609200001; June 11, 2009
- RIVM Normen. Methacrylic acid | Risico's van stoffen ([rivm.nl](#)), last consulted 03-04-2023
- 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.
- Ruijten, 2009. "Assessment of odour announce in chemical emergency management"; M.W.M.M Ruijten.