World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 4

AQUATAIN AMF

(Aquatain Products Pty. Ltd.)

027-001

Safety Assessment

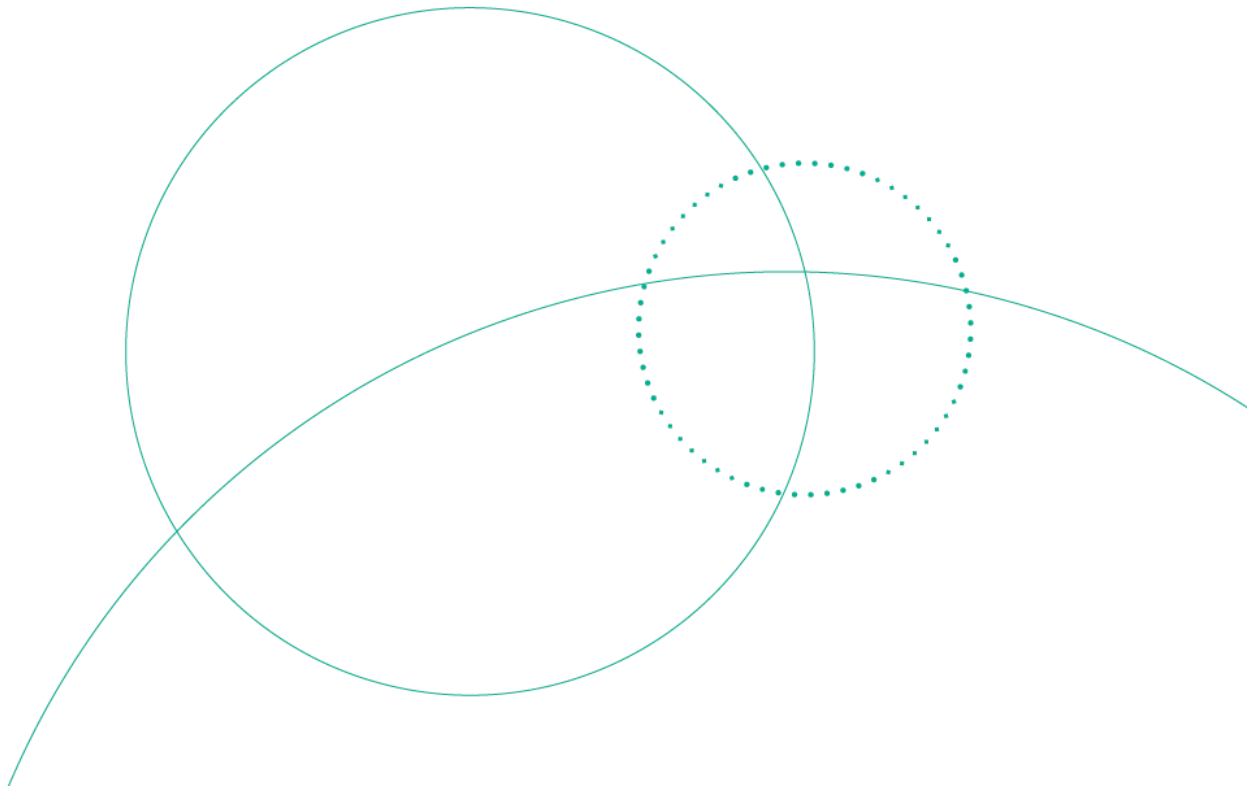

Table of Contents

1 Risk Assessment Summary

1.1 Introduction

The applicant, Aquatain Products Pty Ltd., Australia submitted a Post-Prequalification change application to the World Health Organization Prequalification Unit/Vector Control Products (WHO PQT/VCP) to amend the larvicide product Aquatain AMF (PQ Ref. No 027-001), adding drinking water to the already assessed use sites: large water bodies; including standing water in ponds, smaller water bodies; including drains, gutters, water tanks, and old tires, and in manholes, water traps, and catch basins where high levels of floating debris may be present. The risk assessment conducted under this change application encompasses all prequalified uses for the product and supersedes section 4.1 of the supporting Decision Document published 19 December 2018.

1.2 Product Identification

Applicant:	Aquatain Products Pty Ltd., Lauriston, Victoria, Australia
Product name:	Aquatain AMF
Other names:	N/A
Active ingredient (AI):	Polydimethylsiloxane [78 - 89%]
CAS no.:	63148-62-9
Product type:	Larvicide
Formulation type:	Silicon based liquid
Description of packaging:	
Target application rate:	1 ml/m^2 of water surface = 0.890 g PDMS/m^2 of water surface
	1-5 ml/m^2 of water surface = 0.890 – 4.45 g PDMS/m^2 per manhole/water trap/catch basin
Volume applied:	1 ml/m^2 of surface water = 1 ml/1,000 L water

1.3 Active Ingredient (AI) Statement

Aquatain AMF is a liquid containing 78 to 89% polydimethylsiloxane (synonyms include PDMS, dimethyl polysiloxane, silicone fluid, and dimethyl silicone). The active ingredient (AI) PDMS acts as a physical barrier when applied to water bodies to control mosquito larvae and pupae. The remaining 11-22% is comprised of food-grade material. There is no chemical action against the mosquito larvae. The low surface tension of the silicone film prevents mosquito larvae and pupae from attaching at the surface to breath causing them to drown. The product also deters gravid females from laying eggs on treated surfaces. Larvicide products may be applied to water used for irrigation of food crops, or to treat drinking water supplies.

1.4 Summary of Findings

In this human health risk assessment, the estimated risk ratios for Aquatain AMF are based on the highest concentration of polydimethylsiloxane (maximum concentration 89% or 890 mg AI/ml Aquatain AMF).

The assessment supports the following conclusions:

- The existing toxicology database for Aquatain AMF and the active ingredient Polydimethylsiloxane is adequate for risk assessment and supports the proposed labelled uses of Aquatain AMF up to a concentration of 1 ml Aquatain AMF/m^2 surface drinking water and standing water in small water bodies (drains, gutters, etc.), 1-5 ml per manhole/water trap/catch basin, and 1L per 1000 m^2 of Aquatain AMS applied over large water bodies (i.e. ponds)
- The risk ratios are below 1 for all exposure scenarios and populations.
- The use of Aquatain AMF liquid containing up to 89% Polydimethylsiloxane (PDMS) as a larvicide in surface water, drinking water tanks and other containers,, or in a manhole/water trap/catch basin in the course of vector control does not present any unacceptable risk for operators, residents (adults, children, toddlers, and infants), residents working as operators, or to infants and newborns exposed through breast milk.

2 Human Health Risk Assessment

This human health risk assessment for Aquatain AMF is conducted according to the "A Generic Risk Assessment Model for Insecticides Used for Larviciding and Molluscicding, 2nd edition" (GRAM) (WHO, 2018). Risk assessment involves three steps: Hazard assessment, Exposure assessment and Risk characterization.

- **Hazard assessment** is the identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations are used as starting points for the risk assessment of insecticides. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR), International Programme on Chemical Safety (IPCS), International Agency for Research and Cancer (IARC), United States Environmental Protection Agency (USEPA), European Food Safety Authority (EFSA).
- **Exposure assessment** is assessed in a "guideline scenario" which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. Conservative high-end point estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are covered.
- In **risk characterization**, estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

2.1 Hazard Assessment

2.1.1 The Product – Aquatain AMF

Several acute toxicology studies were conducted with Aquatain AMF. The authors claimed that the studies were conducted according to Good Laboratory Practices and were designed based on OECD guidelines. However, deficiencies in study design and procedure; data recording and reporting; and analytical measurements were noted in most studies. Collectively, the data can be used to support the safety of Aquatain AMF as vector control product.

Aquatain AMF is practically non-toxic by the oral administration (oral LD50 > 2000 mg/kg bw in mice) and non-toxic by dermal application (LD50 > 2000 mg/kg bw in rats). In an inhalation study with rats, the LC50 is 7.3 mg/L/4 hours based on the highest nominal aerosol concentration generated. Topical application of the test material did not result in skin irritation. Aquatain AMF is not an eye irritant based on the results of a study in rabbits. Aquatain AMF is not a skin sensitizer.

Acute toxicity studies conducted with Aquatain AMF are summarized in Table 1.

Table 1. Acute Toxicity of Aquatain AMF

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Mice	$LD_{50} \geq 2000$ mg/kg bw	5	APT, 2017
Acute dermal toxicity	Rat	$LD_{50} \geq 2000$ mg/kg bw	5	Guangdong, 2014
Acute inhalation toxicity	Rat	LC_{50} = 7.3 mg/L/4 hours	3	Guangdong, 2014
Primary dermal irritation	Rabbit	Not irritant	Not classified	JRF, 2015
Primary Eye irritation	Rabbit	Slightly irritant/Reversible	Not classified	JRF, 2015
Skin sensitization, Buehler	Guinea Pigs	Non-sensitizer	Not classified	JRF, 2015

2.1.2 Active Ingredient – Polydimethylsiloxane

The active ingredient (AI) in the product Aquatain AMF is Polydimethylsiloxane (PDMS). This risk assessment relies heavily on toxicity studies conducted on the AI itself as the AI is the active substance that produces a targeted pesticidal effect but can also have the potential to produce toxic biological effects.

PDMS is a polymer and belongs to the group of silicone fluid. Chemically, PDMS is a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $(CH_3)_2SiO$. Toxicology studies have been evaluated by the European Food Safety Authority (EFSA, 2020) and a scientific opinion is available. The toxicity profile of PDMS is presented in Appendix A.

The intent of the hazard assessment of an AI, PDMS (Appendix B), is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. For the active ingredient, PQT/VCP relies on these authoritative evaluations, does not state specific data requirements on behalf of VCP, and focuses on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, the hazard assessment is not exhaustive in its summary of publicly available information characterizing the hazard of the AI. The toxicity database of PDMS has adequate studies for hazard characterization.

2.1.2.1 Polydimethylsiloxane Profile Statement

PDMS was reported to be of low acute toxicity after oral and dermal exposure in rats (LD_{50} > 5000 mg/kg bw). In sub-chronic and chronic toxicity studies in mice, rats and dogs, anal leakage and fur matting were reported. Corneal opacities and inflammation of the cornea were noted in studies using the dietary route of administration. Those effects were related to direct contact with PDMS in the diet and not due to systemic exposure.

2.1.2.2 Acute Toxicity

PDMS has low acute toxicity by the oral and dermal exposure, being classified as GHS Category 5 for acute oral and dermal LD_{50} values. PDMS is in Category 5 for inhalation exposure (LC_{50} = 11.58 mg/L). PDMS is a mild eye and skin irritant but is not a dermal sensitizer. Acute studies were conducted following OECD test guidelines and GLP regulations.

Table 2 Acute Toxicity of PDMS Technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} > 5000 mg/kg	5	ECETOC, 2011
Acute dermal toxicity	Rat	LD_{50} > 2000 mg/kg	5	ECETOC, 2011
Acute Inhalation	Rat	LC_{50} > 695 mg/m^3 = 0.695 mg/L LC50 = 11,582 mg/m^3 = 11.58 mg/L	5	ECETOC, 2011
Dermal irritation	Rabbit	Mild irritant	Not classified	ECETOC, 2011

Eye irritation	Rabbit	Mild irritant	Not classified	ECETOC, 2011
Skin sensitization	Guinea Pigs	Non-sensitizer	Not classified	ECETOC, 2011

2.1.2.3 Absorption, Distribution, Metabolism, and Excretion (ADME)

Absorption, distribution, metabolism and elimination (ADME) studies are not available for PMDS.

Oral absorption: 100% (default value)

Dermal absorption: 10% (default value)

Inhalation absorption: Absorption via the inhalation route is assumed to be 100%. Due to the lack of a long-term inhalation study, the oral equivalent is used for the inhalation risk assessment.

2.1.3 Points of Departure (POD) and Reference Doses (RfD) for the AI

2.1.3.1 Points of Departure

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

2.1.3.2 Reference Doses

A reference dose (RfD) is an estimate of daily oral exposure (acute, aRfD) for a duration of 24 hours or less or chronic oral exposure (cRfD) for a duration of several months to a lifetime that is likely to be without an appreciable risk of deleterious effects during a lifetime. Both an aRfD and a cRfD can be derived from a NOAEL, LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

2.1.3.2.1 Acute reference dose (aRfD)

The US EPA has not established an acute RfD for PDMS.

2.1.3.2.2 Chronic Reference Dose (cRfD)

The US EPA has not established a chronic RfD for PDMS

2.1.3.3 Acceptable Daily Intake (ADI)

JMPR (1974) established an ADI based on the NOAEL of 150 mg/kg bw/day from a rat chronic study. An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the ADI.

ADI = 1.5 mg/kg bw/day

EFSA (2020) established an ADI based on the NOAEL of 1,742 mg/kg bw from a chronic/carcinogenic study in rats (Kawabe et al., 2005). An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the ADI. EFSA panel withdrew the ADI of 1.5 mg/kg bw/day previously established by JMPR.

ADI = 17 mg/kg bw/day

2.1.3.4 Selection of the Tolerable Systemic Dose (TSD)

The PQT/VCP did not select a TSD for acute exposure (TSD_{AC}) since an aRfD for PDMS has not been established.

The PQT/VCP selected the ADI of 17 mg/kg bw/day established by EFSA in 2020 as the TSD for long term risk characterization.

TSD = 17 mg/kg bw/day

2.2 Exposure Assessment

The second step in performing a risk assessment is to estimate exposure to the larvicide, PMDS, in the various groups of people potentially at risk. Exposure must take various parameters into consideration, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality and whether this exposure is intermittent or continuous.

Conservative, high-end estimates of the default distributions are used as defaults in the exposure assessment. The default values may be modified by users of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point estimates or distributions, when applicable. Similarly, application of anthropometric and physiological datasets derived from the true target population, when available, is likely to yield more accurate exposure predictions. The directions for use of this product (Aquatain AMF) and application rate are used to characterize occupational and residential exposure risk for CDW (concentration in drinking water).

The exposure assessment (i.e., exposure calculations) is assessed according to the WHO-GRAM "*Generic Risk Assessment Model for Insecticides Used for Larviciding and Mollusciding" 2nd Edition (2018)*" and chemical-specific data. Exposure assessment includes operator exposure: mixing and loading, application of the insecticide product by washing and maintenance of the equipment, and residential exposure: ingestion exposure from using treated water as drinking water and exposure via breast milk. In the total exposure assessments, all relevant routes and different scenarios are summed to derive the total systemic dose.

Aquatain AMF is a liquid containing 78 to 89% polydimethylsiloxane(PDMS) equivalent to 890 mg PDMS/ml Aquatain AMF. The product Aquatain AMF is intended to be used as a larvicide for control of mosquito larvae and pulpal in various water bodies including drinking water tanks. The target dose of the product is 1 ml Aquatain AMF/ m^2 of surface water or 890 mg PDMS per m^2 of surface water. The volume applied per m^2 is 1 ml, hence the concentration of PDMS in drinking water is 890 mg PDMS/1000 L (since (1 m^2 water equals to 1000 L) or 0.890 mg PDMS/L drinking water or 0.00089 mg/ml drinking water or

0.89 µ/ml drinking water. This application to drinking water tanks and other containers represents the highest exposure-potential, therefore, the use pattern is applied throughout the exposure scenarios.

The following abbreviations and default values are used throughout the exposure assessment*:

Abs-D = Dermal absorption (10%, default)
Abs-P = Respiratory absorption (default = 100%)
Abs-O = Oral absorption (default = 100%)
AT = Average time (default = 365 days)
BW = Body weight (default = 60 kg/adult, 23.9 kg/children, 10 kg/toddlers, 8 kg/infant)
CDW = Concentration in drinking water (890 µg/L)
CF = Concentration of formulation: (890 mg/ml)
Dose $_{Mbw}$=Daily dose to the mother (µg/kg bw/day)
EF= Exposure frequency (default=72 days for operator exposure; For residential exposure =183 days for drinking treated water)
IR=Ingestion rate of milk (default=0.66 kg/day)
NOD= Number of mixing operations per day (default=12)
PPE= Personal protective equipment.
Guideline scenario = 0.1 (90% protection); Lax standard scenario = 1 (no protection)
Sol C = Solubility constant = 0.361 for lipid-soluble chemical (PDMS is a polymer non-soluble in water)
SysD $_{TWA}$= TWA systemic dose (µg/kg bw/day)
SysD $_{MAX}$ = Maximal systemic dose (µg/kg bw/day)
T1/2= First order kinetics half-life of PDMS, 1-day
UE $_{LIQ}$ = Unit exposure for handling liquid formulation (default=0.01mL/operation)
VS_{DERMAL} = The operator may be exposed to small quantities of the product when washing the drum or bottle. Therefore, only a small volume of 1 ml is used in this risk assessment instead of the default of 8.2 ml in GRAM.
WIR = Water ingestion rate (2 Liters/day for adults, children and toddler; 0.75 Liters for infants - GRAM)

2.2.1 Occupational Exposure

2.2.1.1 Operator Exposure during Mixing and Loading of Aquatain AMF

From acute (maximum) exposure

The estimated systemic dose (maximum) of PDMS to operator due to potential acute dermal exposure from mixing and loading is depicted in Table 3:

$$\text{Sys-D}_{MAX} = \frac{UE_{LIQ} \times PPE \times CF \times Abs\text{-}D \times NOD \times 1000}{BW}$$

Table 3. Estimated Daily Systemic Dose to Operator from Dermal Exposure during Mixing and Loading

Guideline Scenario						
UE_{LIQ} (ml/operation)	PPE	CF (mg/ml)	Abs-D (%)	NOD	BW (kg)	Systemic dose (µg/kg/day)
0.01	0.1	890	10	12	60	17.8
Lax Scenario						
0.01	1	890	10	12	60	178.0

From repeated (TWA) exposure

The estimated systemic dose (TWA) of PDMS to operator due to potential repeated dermal exposure from mixing and loading is depicted in Table 4:

$$\text{Sys-D}_{TWA} = \frac{UE_{LIQ} \times PPE \times CF \times NOD \times Abs\text{-}D \times EF \times 1000}{BW \times AT}$$

Table 4. Estimated long term systemic dose (TWA) to operator from dermal exposure during mixing and loading

UE_{LIQ} (mL)	PPE	CF (mg/mL)	NOD	Abs-D (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario								
0.01	0.1	890	12	10	72	60.0	365	3.511
Lax Scenario								
0.01	1.0	890	12	10	72	60.0	365	35.11

2.2.1.2 Operator Exposure During Application, Washing, and Maintenance

From acute (maximum) exposure

The estimated systemic dose (maximum) of PDMS to operator due to potential acute dermal exposure from application, washing and maintenance is depicted in Table 5.

$$\text{Sys-D}_{MAX} = \frac{VS_{DERMAL} \times CF \times PPE \times EF \times Abs\text{-}D \times 1000}{BW \times AT}$$

(Note: C-spray is replaced by CF since the product Aquatain AMF is not sprayed but poured into drinking water)

Table 5. Estimated systemic dose to operator from dermal exposure during application, washing, and maintenance

VS_{dermal} (ml)	CF (mg/ml)	PPE	Abs-D (%)	BW (kg)	Systemic dose (µg/kg/day)
Guideline scenario					
1	890	0.1	10	60	148.3
Lax Scenario					
1	890	1.0	10	60	1483.0

(Note: VS-Dermal: The operator may be exposed to small quantities of the product when washing the drum or bottle. Therefore, only a small volume of 1 ml is used in this risk assessment instead of the default of 8.2 ml in GRAM)

From repeated (TWA) exposure

The estimated systemic dose (TWA) of PDMS to operator due to potential repeated dermal exposure from application, washing and maintenance is depicted in Table 6.

$$\text{Sys-D}_{TWA} = \frac{VS_{DERMAL} \times CF \times PPE \times EF \times Abs\text{-}D \times 1000}{BW \times AT}$$

(Note: C-spray is replaced by CF since the product Aquatain AMF is not sprayed but poured into drinking water)

Table 6. Estimated long-term (TWA) systemic dose to operator from dermal exposure during application, washing, and maintenance							
VS $_{dermal}$ (ml)	CF (mg/ml)	PPE	EF (days)	Abs-D (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
1	890	0.1	72	10	60	365	29.2
Lax Scenario							
1	890	1.0	72	10	60	365	292.0

2.2.1.3 Total operator exposure

Estimated total systemic exposure to operators from dermal exposure from mixing, loading, application, washing, and maintenance is presented below.

Table 6. Estimated total operator exposure from dermal exposure			
Scenario	Dermal exposure		Estimated systemic dose (µg/kg/day)
	Mixing/Loading (µg/kg/day)	Application/Washing/Maintenance (µg/kg/day)	
Estimated TWA (repeated exposure)			
Guideline	3.511	29.2	32.71
Lax	35.11	292.0	327.1
Estimated maximal (acute)			
Guideline	17.8	148.3	166.1
Lax	178.0	1483.0	1661.0

2.2.2 Residential Exposure

2.2.2.1 Oral exposure due to drinking contaminated water

From Acute (maximum) exposure

The estimated systemic dose (maximum) of PDMS to residents from ingestion of treated drinking water is depicted in Table 7.

$$\text{Sys-D}_{MAX} = \frac{\text{CDW x WIR x Abs-O x 1000}}{\text{BW}}$$

Table 7. PDMS estimated systemic dose (maximum) to residents from oral exposure resulting from ingestion of treated drinking water.					
Population	CDW (mg/L)	WIR (Liters/day)	Abs-O (%)	BW (kg)	Systemic dose (µg/kg/day)
Adult	0.890	2	100	60	**29.6**
Children	0.890	2	100	23.9	**74.5**
Toddler	0.890	2	100	10	**178.0**
Infants	0.890	0.75	100	8	**83.4**

From repeated (TWA) exposure

The estimated systemic dose (TWA) of PDMS to residents from ingestion of treated drinking water is depicted in Table 8**.**

$$\text{Sys-D}_{TWA} = \frac{\text{CDW x WIR x Abs-O x EF x 1000}}{\text{BW x AT}}$$

Table 8. PDMS estimated systemic TWA dose to residents from oral exposure resulting from ingestion of treated drinking water.

Population	CDW (mg/L)	WIR (Liters/day)	Abs-O (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Adult	0.890	2	100	183	60	365	**14.87**
Children	0.890	2	100	183	23.9	365	**37.3**
Toddler	0.890	2	100	183	10	365	**89.24**
Infants	0.890	0.75	100	183	8	365	**41.8**

2.2.2.2 Inhalation Exposure

Inhalation exposure is negligible and not of concern.

2.2.3 Exposure via breast milk

Newborns might be exposed to PDMS through breast milk of lactating mother. The estimated systemic dose to the newborn is calculated based on the estimated systemic dose to the mother as a resident operator. WHO does not approve nor recognize a scenario where a nursing or lactating mother is working as an operator. To illustrate the worst-case exposure scenario, this scenario has been evaluated.

Estimates for systemic TWA and maximal doses from exposure via breast milk are calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{\text{SolC x Dose}_{Mbw}\text{ x T}_{1/2}\text{ x IR x Abs-O}}{\text{BW}}$$

Mother's doses (Dose_{Mbw}) entail a worst-case scenario where the mother is considered both a resident and works as an operator. For determining the exposure as an operator, the lax scenario (assuming no personal protective equipment) is used as a worst-case scenario for calculating the mother's dose. For the resident, it includes oral and dermal exposure from drinking treated water.

Dose_{Mbw} = Operator (mixing/loading + application + washing+ maintenance) + Resident (oral treated water)

- Dose_{Mbw} TWA = 327.1 + 14.87 = 341.97 µg/kg bw/day
- Dose_{Mbw} Maximum = 1661.0 + 29.6 = 1690.6 µg/kg bw/day

Table 9: PDMS estimated systemic dose from exposure via breast milk.

Population	SolC	$Dose_{MBW}$ (µg/kg bw)	$T_{1/2}$ (days)	IR (kg/day)	Abs-O (%)	BW (kg)	Systemic dose (µg/kg/day)
TWA Scenario							
Newborns	0.361	341.97	1	0.66	100	4.2	19.40
Maximum Scenario							
Newborns	0.361	1690.6	1	0.66	100	4.2	95.90

2.3 Risk Characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring from the use of the larvicide under defined exposure conditions. Risk characterization consists of comparing the estimate of total exposure (i.e., estimated systemic dose) with the TSD established in the hazard assessment. The TSD is the same as the ADI or the cRfD established for the active ingredients (WHO, 2018).

$$\text{Risk Ratio} = \frac{\text{Total TWA systemic dose (µg/kg bw/day)}}{\text{TSD (µg/kg bw/day)}}$$

When the active ingredient has significant acute toxicity, the aRfD is used as the TSD_{AC} to calculate risk ratios as shown below (WHO, 2018).

$$\text{Ratio} = \frac{\text{Total maximal systemic dose}}{TSD_{AC}\ \text{(µg/kg bw/day)}}$$

When the ratios are less than 1, the health risk is deemed acceptable. Ratios greater than 1 may indicate possible health risks, in which case steps may be taken to reduce the risk, such as changing the recommended operational conditions or the amount of active ingredient in the technical product. A risk benefit analysis in which the risks of potential toxicity are compared with potential health benefits(disease prevention) may be needed in some cases (WHO, 2018).

Table 10. Risk Characterization for all Populations and Exposure Scenarios

Population	Operator exposure (dermal and inhalation) (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Total operator exposure – TWA scenario – Repeated exposure			
Adult – guideline	**32.71**	**17,000**	**0.002**
Adult - lax	**327.1**	**17,000**	**0.019**
Total operator exposure – maximal scenario – Acute exposure			
Adult – guideline	**166.1**	**17,000**	**0.009**
Adult - lax	**1661.0**	**17,000**	**0.097**
Total operator/residential exposure – TWA scenario – Repeated exposure			
Adult – guideline	**47.58**	**17,000**	**0.003**
Adult - lax	**341.97**	**17,000**	**0.020**
Total operator/residential exposure – Maximal scenario – Acute exposure			
Adult – guideline	**195.7**	**17,000**	**0.0115**
Adult - lax	**1690.6**	**17,000**	**0.099**

Table 10. Risk Characterization for all Populations and Exposure Scenarios			
Population	**Residential exposure (drinking water) (µg/kg bw/day)**	**TSD (µg/kg bw/day)**	**Risk ratio**
Total exposure – TWA scenario			
Adult	**14.87**	**17,000**	**0.0008**
Children	**37.3**	**17,000**	**0.002**
Toddler	**89.24**	**17,000**	**0.005**
Infant	**41.8**	**17,000**	**0.002**
Total exposure – maximal scenario			
Adult	**29.6**	**17,000**	**0.002**
Children	**74.5**	**17,000**	**0.004**
Toddler	**178.0**	**17,000**	**0.010**
Infant	**83.4**	**17,000**	**0.004**
TWA Total exposure – breast milk – residential			
Newborn	**19.40**	**17,000**	**0.001**
Maximal Total Exposure – breast milk – residential			
Newborn	**95.90**	**17,000**	**0.0056**

In summary,

- For operators (mixing/loading/applying/maintenance), the risk ratios are all below 1.
- For residents (drinking of treated water), the risk ratios are below 1 for all populations of concern (adults, children, toddlers and infants)
- For resident/operator, the risk ratios are all below 1.
- For the potential exposure via breast milk of mother as resident, the risk ratio is below 1.

2.4 Conclusions

The use of Aquatain AMF liquid containing up to 89% Polydimethylsiloxane (PDMS) as a larvicide in drinking water, in large and small water bodies, and in areas where stagnant water may be present, in the course of vector control does not present any unacceptable risk for operators, residents (adults, children, toddlers, and infants), residents working as operators, or to newborns exposed through breast milk. The risk ratios are below 1 for all exposure scenarios and populations.

References

APT Testing & Research PVT Ltd., India, 2017: Acute oral toxicity of Aquatain AMF in mice. Report No. CH081/1415/0292a, dated Jan 24, 2017.

APT Testing and Research PVT Ltd., India, 2017: Test for skin irritation of Aquatain AMF in rabbits. Report No. CH081/1415/0293e, dated Jan 24, 2017.

APT Testing and Research PVT Ltd., India, 2017: Test for eye irritation of Aquatain AMF in rabbits. Report No. CH081/1415/0293g, dated Jan 24, 2017.

Dow Corning, 1989. A 90-day subchronic oral toxicity study with polydimethylsiloxane fluids in the rat. Midland, MI, USA, Dow Corning, Toxicology Department, 13 July 1989

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), 2011. JACC Report No. 55 – Linear Polydimethylsiloxanes, CAS No. 63148-62-9 (Second Edition), Brussels, December 2011.

EFSA (European Food Safety Authority), 2020. Scientific Opinion; Re-evaluation of PDMS as a food additive, EFSA Journal 18(5): 6107.

GHS, 2017. United Nations Globally Harmonized System of Classification and Labelling of Chemicals.

Guangdong Provincial Test Center for Occupational Health, China, 2014: Aquatain AMF acute dermal toxicity test in rats. Report No. DL 1400112 dated Oct 10, 2014.

Guangdong Provincial Test Center for Occupational Health, China, 2014: Aquatain AMF acute inhalation toxicity test in rats. Report No. DL 1400113 dated Oct 10, 2014.

JAI Research Foundation, India, 2015: Acute dermal irritation study of Aquatain AMF in rabbits. Report No. 406-1-01-12159, dated Nov 14, 2015.

JAI Research Foundation, India, 2015: Acute eye irritation study of Aquatain AMF in rabbits. Report No. 407-1-01-12160, dated Nov 14, 2015.

JAI Research Foundation, India, 2015: Skin sensitization study of Aquatain AMF in Guinea Pigs. Report No. 408-1-01-12161, dated Dec 4, 2015.

JECFA, 1974. Evaluation of certain food additives, Eighteen Report, TRS 557 report 18th meeting.

JECFA, 2011. Polydimethylsiloxane, Combined Compendium of Food Additive Specifications, Monograph. 11.

Kawabe et al., 2005. Lack of carcinogenicity of silicone resin (KS66) in Fisher F344 rats. Food and Chemical Toxicology, 43.

WIL Research, Ashland, OH, 2003: PDMS chronic toxicity study in rats. Report No. 51032, dated 2003.

WHO, 2018. "*A Generic Risk Assessment Model Insecticides Used for Larviciding and Mollusciding, 2nd edition"* (GRAM).

Appendices

Appendix A. Toxicity Profile: Polydimethylsiloxane Technical

Table A1. Acute Toxicity of PDMS Technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} > 5000 mg/kg	5	ECETOC, 2011
Acute dermal toxicity	Rat	LD_{50} > 5000 mg/kg	5	ECETOC, 2011
Acute Inhalation	Rat	LC_{50} = 11.58 mg/L	5	ECETOC, 2011
Dermal irritation	Rabbit	Mild irritant	Not classified	ECETOC, 2011
Eye irritation	Rabbit	Mild irritant	Not classified	ECETOC, 2011
Skin sensitization,	Guinea pigs	Non-sensitizer	Not classified	ECETOC, 2011

Subchronic, Chronic, and Carcinogenicity Studies

Table A2. Summary of Subchronic, Chronic, and Carcinogenicity Studies with PDMS

Study dose levels	Results (mg/kg bw/day)	Reference
28-day dietary study, Fischer 344 rats Dose levels: 0, 10000, 25000, 50000 and 100000 ppm (equal to 0, 950/1013, 2428/2562, 4986/5286, and 10615/11325 mg/kg bw/day in males/females, respectively	Increased incidences of matting of the fur at the highest dose tested and corneal opacities were observed at all dose levels suggesting a direct contact with PDMS in the diet. Mean food consumption was increased in the two highest dose groups. Increased in relative kidney weights were noted in males at 50,000 and 100000 ppm groups	EFSA, 2020
90-day dietary oral toxicity study, Sprague Dawley rats Dose levels: 0, 1, 5, and 10% in the diet (equivalent to 0, 900, 4500 and 9000 mg/kg bw/day of PDMS)	Slight of marked anal leakage of fluid was observed in some groups. Corneal opacities and inflammation of the cornea were found in treated groups in a non-dose related manner. Two incidences of lymphatic lymphomas were found in treated males at 9000 mg/kg bw/day and one undifferentiated lymphoma in one male at the 900 mg/kg bw/day dose level. Systemic NOAEL: not determined	EFSA, 2020
90-day dietary oral toxicity, male Sprague Dawley rats Dose level: 9000 mg/kg bw/d of PDMS	This study was conducted to either confirm or disregard the findings of lymphomas in males in the previous study. Slight increase in food consumption was noted. No lymphomas were found in male rats.	EFSA, 2020
90-day dietary oral toxicity study, Fischer 344 rats Dose levels: 0, 5000, 10000, 25000 and 50000 ppm (equivalent to 0, 351/395, 718/792, 1780/2025 and 3773/4348 mg/kg bw in males/females, respectively.	Matting of fur and corneal opacities were noted at all dose levels, possibly a result of direct contact with PDMS in the diet. Total cholesterol, high density lipoprotein and phospholipid were decreased in all male groups except at the lowest level of 351 mg/kg bw (5000 ppm). The systemic NOAEL = 351 mg/kg bw and the LOAEL was 718 mg/kg bw.	EFSA, 2020

Table A2. Summary of Subchronic, Chronic, and Carcinogenicity Studies with PDMS		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
90-day oral feeding study, CD-1 mice Dose levels: 0, 5 and 10% in the diet (equivalent to 0, 10,000 and 20,000 mg/kg bw PDMS/day	Test material = PDMS fluid No treatment related adverse effects were found. Slight to moderate anal leakage and matting of fur were found but were not considered as adverse. Systemic NOAEL = 20,000 mg/kg bw/day Systemic LOAEL = not determined	EFSA, 2020
13-week oral, dogs Doses: 0, 120, 380 or 1200 mg/kg bw/day	Dogs (3/sex/group) received DC Medical antifoam. Soft stools were reported in all treated groups including the control. Mean weight of thyroid, heart and pituitary were increased at 1200 mg/kg dose level. Mean weight of spleen was increased at 380 and 1200 mg/kg bw/day dose levels.	EFSA, 2020
120-day oral (capsule) study, dogs Doses: 300 mg/kg bw/day	Dogs (4/sex/group) received 300 mg/kg bw for 120 days followed by 5 days of recovery period. No changes in haematological parameters and no treatment related findings were noted at macroscopic and microscopic examination. The systemic NOAEL = 300 mg/kg bw and the systemic LOAEL = not established	EFSA, 2020
76-week Chronic Toxicity Dietary Study in mice Treated with a "silicone antifoam agent containing 94% PDMS. Doses: 0, 0.25, and 2.5% corresponding to 0, 580 and 5800 mg/kg bw/day for PDMS.	The incidence of stomach ulcer was statistically increased in mid-dose males but not in high dose males. The incidence of ovary cysts was increased in mid-dose females but not in high dose group. There was no evidence of carcinogenic effect in both males and females	EFSA, 2020
2 year combined chronic/carcinogenic oral study, Fischer 344 rats (90/sex/group) Doses: 0, 100, 300 and 1000 mg/kg bw/day of a PDMS fluid	Corneal opacity and keratitis were noted in all groups affecting both males and females; Significant increase in findings of nasolacrimal duct inflammation was found in high dose males; A statistically significant increase in pancreatic islet cell adenomas was recorded in high dose males but the incidence was still within the historical control range for Fischer 344 rats. No evidence of carcinogenic effect in both male and female rats	EFSA, 2020
26-month combined chronic/carcinogenicity oral dietary study, Fischer 344 rats Doses: PDMS fluid at 0, 1.25 and 5% (equivalent to 0, 530/445 and 2234/1894 mg/kg bw in males/females, respectively	50 animals/sex/group No treatment related changes noted in clinical observations, survival rates, food intake and haematological parameters. Decreased liver weight was noted in high dose males but of no toxicological concern. No treatment related increased incidences of neoplastic lesions were found. Systemic NOAELs = 1894 (females) and 2234 mg/kg bw/day (males). Since the test material contained 92% of PDMS, these NOAELs correspond to 1742 and 2055 mg PDMS/kg bw/day for females and males, respectively. No evidence of carcinogenic effect in both male and female rats.	Kawabe et al., 2005 (as cited in EFSA, 2020)

Developmental Toxicity and Reproduction Studies

Table A3. Summary of Developmental Toxicity and Reproductive Studies with PDMS

Study dose levels	Results (mg/kg bw/day)	Reference
Three-Generation Reproduction Toxicity Study in Rats. Doses: 0, 0.01 or 0.1% of a foam in the diet (equivalent to 0, 4.5 or 45 mg/kg bw/day of PDMS) Study started with weanling rats (30 females and 10 males per group)	Parental systemic NOAEL = 45 mg/kg bw/day Parental systemic LOAEL = not established Reproductive NOAEL = 45 mg/kg bw/day Reproductive LOAEL = not established Offspring NOAEL = 45 mg/kg bw/day Offspring LOAEL = not established	EFSA, 2020
Developmental Toxicity Study in Wistar Rats Oral Administration (Gavage). Doses: 0, 300 or 1000 mg/kg/day of a fluid containing PDMS from gestation days 6 to 15.	Maternal tox NOAEL = 1000 mg/kg bw/day (HDT) Developmental tox NOAEL = 1000 mg/kg bw/day Maternal tox NOAEL and LOAEL = not established (insufficient data reported to establish NOAEL and LOAEL)	Kennedy et al., 1976 (as cited in EFSA, 2020)
Developmental Toxicity Study in New Zealand White Rabbits Oral Administration (Dietary). Doses: 0, 0.5. 1.0 or 2.5% of an antifoam containing PDMS (equivalent to 0, 152, 303 or 756 mg/kg/day) given from gestation days 6 to 19.	Maternal tox NOAEL and LOAEL = not established Developmental tox NOAEL and LOAEL = not established (insufficient data reported to establish NOAEL and LOAEL	EFSA, 2020

Genotoxicity Studies

Table A4. Summary of Genotoxicity Studies with PDMS

Study dose levels	Results	Reference
Bacterial reverse mutation assay, Ames Dose range: 33 to 10,000 ug/plate with and without metabolic activation	Negative in S. typhimurium and E. Coli up to 10,000 ug/plate with and without metabolic activation	EFSA, 2020
In-vitro mammalian cell gene forward mutation in CHO cells Dose range: 39.1 to 5000 ug/ml with and without metabolic activation	Did not induce gene mutation at the HPRT locus in CHO cells	
In-vivo micronucleus assay – Bone marrow cells in mice Dose range: 0 – 2000 mg/kg/day	Negative in producing micronuclei in mice bone marrow – Not a clastogen	EFSA, 2020
Dominant lethal assay in mice Dose: single intraperitoneal injection at 5000 or 10000 mg/kg bw	No mutagenic potential was reported	Kennedy et al., 1976 (as cited in EFSA, 2020)

Neurotoxicity Studies

No studies available

Metabolism Studies

Table A5. Summary of Metabolism Studies with PDMS

Study dose levels	Results (mg/kg bw/day)	Reference

Oral metabolism study, Fischer 344 rats. Single dose of radioactive PDMS at 1000 mg/kg.	Majority of radioactivity was excreted, recovery was 93.4 and 91.% in females and males, respectively. 99.9% and 99.6% were recovered in females and males feces, respectively.	EFSA, 2020
Oral metabolism study, Rhesus monkeys Single dose of radioactive PDMS at 1.15, 13.7 or 18.0 mg/kg bw.	Approximately 2.1 to 2.5% was recovered in urine and 80 to 92% in the feces (over 92 hours)	EFSA, 2020

Dermal Absorption Studies

No data available

Appendix B: Hazard Assessment

1 Introduction to Polydimethylsiloxane

The use of vector control products (VCPs) is critical in the protection of global human health by combatting and preventing the transmission of major vector-borne diseases. Through the procedures of Prequalification Unit Vector Control Product Assessment Team (PQT/VCP), VCPs and public health pesticide active ingredients are assessed to determine that they can be used safely and effectively and are manufactured to a high-quality standard. The intent of the hazard assessment of each active ingredient (AI) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. PQT/VCP relies on these authoritative evaluations, focusing on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, this hazard assessment is not exhaustive in its summary or assessment of publicly available information characterizing the hazard of the AI.

Polydimethylsiloxane is a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $(CH_3)_2SiO$ and stabilized with trimethylsiloxy end-blocking units of the formula $(CH_3)_3SiO$. Its chemical formula is $(CH_3)_3$-Si-[O-Si$(CH_3)_2$]n-O-Si$(CH_3)_3$. Synonyms include PDMS, dimethyl polysiloxane, silicone fluid, silicone oil and dimethyl silicone. Polydimethylsiloxane (PDMS) polymers have many industrial and domestic applications, such as being components in polishes, waxes, paints and personal care products. PDMS is authorized as food additives in the European Union (EU) according to Annex II and Annex III of Regulation (EC) No. 1333/2008 on food additives. PDMS is indicated in the FDA Inventory of Food Contact Substances Listed in 21 CFR. PDMS is also used as a larvicide acting as a physical barrier when applied to water bodies to control mosquito larvae and pupae. There is no chemical action against the mosquito larvae. The low surface tension of the silicone film prevents mosquito larvae and pupae from attaching at the surface to breath causing them to drown. The product also deters gravid females from laying eggs on treated surfaces. Larvicide products may be applied to water used for irrigation of food crops or to treat drinking water supplies.

A scientific opinion on PDMS is available from the European Food Safety Authority (EFSA, 2020) and an annual summary report is available from the World Health Organization (WHO, 2011). The Polydimethylsiloxane toxicity database contains a complement of toxicity studies used to develop the hazard characterization and were considered in designating the points of departure (PODs).

2 Hazard Characterization

Only studies relevant to the hazard evaluation are discussed, for a full description of all toxicology studies related to the active ingredient, the reader is referred to the references cited. There is sufficient information on the toxicity of the active ingredient, Polydimethylsiloxane technical, to conduct a human health hazard assessment. Administration of PDMS to rats, mice, and dog by the oral route resulted in no overt signs of systemic toxicity and no histopathological findings. The primary adverse effects noted in all rodents feeding studies were corneal inflammation and corneal opacity due to direct contact with PDMS in the diet. No neoplastic lesions were identified following chronic and carcinogenicity studies in either mouse or rat. Exposure to PDMS demonstrates that no treatment related developmental toxic effects were noted in both rats and rabbits. No adverse reproductive effects were found in a 3-generation reproduction study with rats. There is no evidence to suggest that PDMS is mutagenic or clastogenic. Although no immunotoxicity and neurotoxicity studies were submitted, the available data does not indicate any likeliness that PDMS is toxic to the immune system or the nervous system.

2.1 **Acute Toxicity**

PDMS is practically non-toxic by the oral administration (LD_{50} > 5000 mg/kg bw), by dermal application (LD_{50} > 5000 mg/kg bw) and by inhalation (LC_{50} > 13 mg/L). These findings are classified as Category V by the United Nations Globally Harmonized System of Classification (GHS, 2017). PDMS is a mild eye irritant and mild skin irritant (GHS Category Not Classified) and is not a skin sensitizer (GHS Category Not Classified). Acute studies were conducted following OECD guidelines and GLP regulations.

2.2 **Subchronic Toxicity**

In a 28-days oral feeding study, Fischer 344 rats (10 animals/sex/group) were given a “DC 200 fluid” in the diet at 0, 10,000, 25,000, 50,000 and 100,000 ppm equivalent to 0, 950/1,013, 2,428/2,562, 4,986/5,286, and 10,615/11,325 mg/kg bw/day. Corneal opacities were noted in all treated and control groups. Hyperplasia and granulomatous inflammation of the corneal stroma were present in all treated groups in a dose-related manner and these lesions were not found in control rats. The study authors indicated that the findings in the corneal were due to direct contact with PDMS in the diet. Mean food consumption was increased in 25,000 ppm males and in both males and females of the 50,000 and 100,000 ppm groups.

In a 90-day feeding study (Dow Corning, 1989), PDMS fluids at viscosities of 35, 350 or 1000 cSt were used. Each fluid was mixed in the diet at 1%, 5%, or 10% (equivalent to 0, 900, 4500 and 9000 mg PDMS/kg bw/day) and fed to groups of 20 male and 20 female rats each. Two control groups (20 rats/sex/group) received basal diet. Animals were observed daily for signs of toxicity. Body weights and feed consumption were measured weekly. Clinical chemistry and hematology were measured and necropsy performed at study termination. Ophthalmology was recorded. Histopathologic examination of organs was performed. There were no overt signs of systemic toxicity. No treatment related effects on body weights, clinical chemistry, hematology, and organ weights were noted. Significantly higher food consumption was observed in the 5 and 10% groups. Three lymphomas were found in treated males – two lymphatic lymphomas in males given 10% and 1 undifferentiated lymphoma in a male given 1%. Necropsy revealed increased incidences of opacity and neovascularization of the cornea in all treatment groups. Most animals with corneal lesions showed minimal to mild chronic inflammation of the cornea, and mineralization was also present in some animals. The corneal lesions were present in a non-dose-related manner. The Joint FAO/WHO Expert Committee on Food Additives concluded that the ocular lesions

noted in this study as well as in previous oral studies with PDMS were caused by direct ocular contact with PDMS in feed or feces or through grooming of contaminated fur. Therefore, the ocular effects observed in short- and long-term toxicity studies were not relevant to the establishment of the ADI (EFSA, 2020).

An additional 90-day study was conducted in Fischer 344 male rats to confirm the findings of lymphomas in the previous study. The study consisted of 2 control groups and a treated group at 9000 mg/kg bw/day. Higher food consumption was noted but no lymphoma was found (EFSA, 2020).

In a 90-day oral feeding study, Fischer 344 rats (15/sex/group) were given "DC 200 fluid" in the diet at 0, 5,000, 10,000, 25,000 and 50,000 ppm (equivalent to 0, 351/395, 718/792, 1,780/2,025, and 3,773/4,348 mg/kg bw/day PDMS). Corneal opacities were noted in all treated groups. Matting of the fur was observed in all treated animals and could be related to direct contact with PDMS in the diet. Increased in food consumption was noted at 10,000, 25,000 and 50,000 ppm. Mean total cholesterol, high density lipoprotein and phospholipid levels were significantly increased in all males treated groups except at the 5000-ppm dose level. The systemic NOAEL could be established at 5000 ppm (351/395 mg/kg bw/day) and the systemic LOAEL at 10,000 ppm (718/792 mg/kg bw/day).

In a 90-day oral study in CD-1 mice, groups of 15/sex/group were administered PDMS at 0, 5 and 10% in the diet equivalent to 0, 10,000 and 20,000 mg/kg bw/day of PDMS (EFSA, 2020). Animals were observed daily for clinical signs, behavioral changes and mortality. Body weights and food consumption were recorded weekly. At terminal, major organs were collected, weighed and examined microscopically. Slight to moderate anal leakage of fluid was observed in the 10% group. Food consumption was significantly increased in both treatment groups. No histopathologic findings were found. The systemic NOAEL could be established at 20,000 mg/kg bw/day and the systemic LOAEL could not be determined.

A 13-week oral toxicity study was conducted in dogs (3 animals/sex/group). Dogs received 0, 120, 380 or 1,200 mg/kg bw/day. Soft stool was recorded in all treated groups. Mean weight of the thyroid, heart and pituitary was increased at 1,200 mg/kg bw/day dose level. Mean weight of spleen was increased at the 380 and 1,200 mg/kg bw/day dose levels. No gross or histopathologic findings were reported. A systemic NOAEL could be established at 120 mg/kg bw/day and the systemic LOAEL at 380 mg/kg bw/day.

A 120-day oral toxicity was conducted in dogs (4 dogs/sex/group). Dogs received 300 mg/kg bw/day PDMS for 120 days followed by 5 days of recovery. Decreased body weight was noted in the first 3-week of treatment but recovered during the following weeks. No changes in hematologic, macroscopic or microscopic findings.

2.3 **Chronic Toxicity and Carcinogenicity**

In a 76-week oral feeding study, mice (40 to 50/sex/group) were given a "silicone antifoam agent" (containing 94% PDMS) in the diet at0, 0.25, and 2.5% (equivalent to 0, 580 and 5800 mg/kg bw/day. Five male and female mice at the 2.5% dose were transferred at week 75 to a control diet for 8 days prior to sacrifice. The incidence of superficial ulcer of the stomach was significantly increased in the mid-dose group but not at the highest dose. The incidence of cysts in the ovaries was significantly increased in mid-dose females but not at the highest dose. There was no increased incidence of neoplastic findings.

PDMS was administered in the diet of Fischer 344 rats for 12 and 24 months at dose levels of 0, 100, 300 or 1000 mg/kg bw (WIL, 2003). There were no significant findings on body weights, feed consumption,

organ weights, ophthalmologic findings, clinical pathology, gross necropsy findings and histopathologic findings. The incidence of corneal opacities was increased in high dose males and in females in the mid and high dose groups. There were no test article related neoplastic or pre-neoplastic findings after 24 months of exposure. In the 1000 mg/kg group, there was an increase in the incidence of islet cell adenomas of the pancreas of male rats, but the incidence was still within the historical control range for Fischer 344 rats. Furthermore, in the absence of similar findings in high dose females and in the presence of high incidence of pancreas islet cell adenomas in the control group, the significance of the finding of pancreas islet cell adenomas in the 1000 mg/kg group is questionable. There was no indication of oncogenicity potential after 24 months of feeding up to 1000 mg/kg bw (WHO, 2011; EFSA, 2020).

In a 26-month toxicity study in Fischer 344 rats, PDMS was administered in the diet at 0, 1.25 and 5% (equivalent to 0, 530/445, 2234/1894 mg/kg bw/day in males/females, respectively. No overt signs of toxicity were noted up to the highest doses tested. No increase in the neoplastic findings was reported. The systemic NOAEL was established at 1,894 mg/kg bw/day (females) and 2,234 mg/kg bw/day (males). Since the test material contained 92% of PDMS, these NOAELs correspond to 1,742 and 2,055 mg PDMS/kg bw/day for females and males, respectively (Kawabe et al., 2005 as cited in EFSA, 2020).

2.4 **Developmental Toxicity**

In a developmental toxicity study, female rats (strain, number of animals/groups, age and body weight not specified) were given “DC 700 vapor booster pump fluid” by oral gavage at 0, 300 or 1,000 mg/kg bw per day during GDs 6–15 (Kennedy et al., 1976 as cited in EFSA, 2020). Twenty females were sacrificed, fetuses were taken by Caesarean section and uterus and ovaries were examined. The number of implantation sites, and live and dead pups were counted. One-third of the pups were examined for visceral anomalies and the remaining pups were stained and examined for skeletal abnormalities. No adverse effects were reported. The reporting of the study was very limited (EFSA, 2020).

In a developmental toxicity study, time-mated New Zealand white rabbits (n = 20–22 per group) were fed 0, 0.5, 1.0 or 2.5% DC Antifoam A in the diet (equivalent to 0, 152, 303 or 756 mg/kg bw per day) from GD 6 through the morning of GD 19 (EFSA, 2020). No clinical signs, differences in body or liver weight were observed in the does. The number of resorptions, and fetal weight were not affected. No treatment-related effects were observed at fetal external, visceral or skeletal examination. The author concluded that no treatment-related developmental effects were observed. Since only an abstract was available, this study cannot be used for hazard assessment (EFSA, 2020).

Although the developmental toxicity studies are limited, using a weight of evidence approach and based on the physical-chemical characteristic of Polydimethylsiloxane, there is no evidence to suggest that PDMS is a developmental toxicant.

2.5 **Reproduction Toxicity**

A 3-generation reproduction study was initiated with weanling rats (30/sex/group) at 0, 0.01 or 0.1% of PDMS in the diet corresponding to 0, 4.5 or 45 mg/kg bw/day of PDMS). Animals were mated after 16 weeks. Ten males and 30 females were chosen randomly from offspring of each group (generation 1). Generation 1 animals were mated after 16 weeks and ten males and 30 females were chosen randomly from offspring of each group (generation 2). The number of litters born in each group and the number of pups in each litter was recorded and litters containing more than eight pups were culled to that number.

Offspring survival rate at post-natal day 21 was recorded. Hematological examinations (total erythrocyte, lymphocyte, monocyte and granulocyte counts, and hemoglobin) were performed after 25 weeks in generation I and after 20 weeks in generation II. Surviving animals were sacrificed after 2 years (generation 0), 28 weeks (generation I) and 23 weeks (generation II) and 3 females from each group of each generation were chosen randomly for histological examination. Organ weights (heart, spleen, liver, kidneys, stomach, intestine, caecum, adrenals, ovaries and uterus) were recorded for 10 females of each group in generation I and II, and testes weight were recorded for males. Significant differences in body weight between control and treated groups were noted in generation I and II without a consistent trend to decreased or increased weight between particular groups; the study authors concluded that the observed changes were not of toxicological significance. Relative to reproductive performance, the survival rate of the generation 0 offspring was slightly higher in the high dose group as compared to controls, but lower ($p < 0.01$) in the generation I offspring; the biological significance of this finding is doubtful. No other significant differences were reported (EFSA, 2020). Reproduction studies with rats did not demonstrate any adverse effects of PDMS on fertility, gestation, peri- or post-natal development (ECETOC, 2011). The parental systemic NOAEL and reproductive NOAEL could be established at 45 mg/kg bw/day. The parental LOAEL and reproductive LOAEL are undetermined.

2.6 **Genotoxicity**

In vitro and *in vivo* genotoxicity studies did not indicate that PDMS has mutagenic activity (EFSA, 2020). In bacterial gene mutation assays (Ames assays), PDMS did not induce gene mutation in *Salmonella* and *E. Coli* up to a concentration of 10,000 µg/plate in the presence and absence of metabolic activation. In an *in vitro* mammalian cell gene mutation assay, PDMS did not induce mutations in CHO cells in both the presence and absence of metabolic activation. In two *in vivo* micronucleus assays in mice, no clastogenic or mutagenic activity was detected in peripheral blood cells after intraperitoneal administration of PDMS. In a dominant lethal assay with mice, animals were given a single intraperitoneal injection of PDMS at 5,000 or 10,000 mg/kg bw and no mutagenic potential was detected (EFSA, 2020).

2.7 **Neurotoxicity**

No data available.

2.8 **Absorption, Distribution, Metabolism, and Excretion (ADME)**

2.8.1 Oral route studies

Oral absorption of PDMS was very limited after administration to mice, rats, and monkeys. In a study with Fischer 344 rats, PDMS was given by gavage at 1000 mg/kg bw. More than 99.9% of the orally administered PDMS was excreted unchanged in the feces. The recovery was 93.4% in females and 91.0% in males (EFSA, 2020). Three Rhesus monkeys received a single oral gavage of ^{14}C labelled PDMS at dose levels of 1.15, 13.7 or 18.0 mg/kg bw. The majority of the radioactivity was recovered in the feces. The parent compound was excreted unchanged (EFSA, 2020). Absorption via the oral route is assumed to be 100%. Due to the lack of a long-term inhalation study, the oral equivalent is used for the inhalation risk assessment (100%). Based on the dermal LD_{50} value (> 5000 mg/kg bw), dermal penetration is not of concern. In this risk assessment a default value of 10% is used for dermal absorption (GRAM).

2.8.2 Dermal route studies

No study available.

Due to the lack of a long-term dermal study, a dermal absorption of 10% is used for risk assessment purposes (GRAM).

2.8.3 Inhalation route studies

No study available.

Due to the lack of a long-term inhalation study, oral exposure of 100% is used for risk assessment purposes.

3 Points of Departure (POD), Reference Doses (RfD), and Cancer Classification

3.1 **Points of Departure**

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

3.2 **Reference Doses**

A reference dose (RfD) is an estimate of daily oral exposure (acute, aRfD) for a duration of 24 hours or less or chronic oral exposure (cRfD) for a duration of several months to a lifetime that is likely to be without an appreciable risk of deleterious effects during a lifetime. Both an aRfD and a cRfD can be derived from a NOAEL, LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

3.2.1 Acute Reference Dose (aRfD)

The US EPA has not established an acute RfD for PDMS.

3.2.2 Chronic Reference Dose (cRfD)

The US EPA has not established a chronic RfD for PDMS.

3.2.3 Acceptable Daily Intake (ADI)

JMPR (1974, 2011) established an ADI based on the NOAEL of 150 mg/kg bw/day from a rat chronic study. An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the ADI.

ADI = 1.5 mg/kg bw/day

EFSA (2020) established an ADI based on the NOAEL of 1,742 mg/kg bw from a chronic/carcinogenic study in rats (Kawabe et al., 2005). An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the ADI. EFSA panel (2020) withdrew the ADI of 1.5 mg/kg bw/day previously established by JMPR (2011).

ADI = 17 mg/kg bw/day

3.3 **Cancer Classification**

JMPR (1974) and EFSA (2020) concluded that Polydimethylsiloxane was not carcinogenic in mice or rats and was unlikely to be genotoxic based on the chronic carcinogenicity and genotoxic studies.