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**NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME  
(NICNAS)**

**FULL PUBLIC REPORT**

**Butanedioic acid, 1-[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl] ester  
(INCI: Menthyl succinate)**

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment, Water, Heritage and the Arts.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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**Director  
NICNAS**

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**FULL PUBLIC REPORT****Butanedioic acid, 1-[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl] ester  
(INCI: Menthyl succinate)****1. APPLICANT AND NOTIFICATION DETAILS**

## APPLICANT(S)

Johnson & Johnson Pacific Pty Ltd (ABN 73 001 121 446)  
45 Jones Street  
ULTIMO NSW 2007

## NOTIFICATION CATEGORY

Limited-small volume: Chemical other than polymer (1 tonne or less per year).

## EXEMPT INFORMATION (SECTION 75 OF THE ACT)

No details are claimed exempt from publication.

## VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)

Variation to the schedule of data requirements is claimed as follows:

Boiling point, Density, Vapour pressure, Water solubility, Hydrolysis as a function of pH, Partition coefficient, Adsorption/Desorption, Dissociation constant, Particle size, Flash point, Flammability limits, Autoignition temperature.

## PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)

None

## NOTIFICATION IN OTHER COUNTRIES

None

**2. IDENTITY OF CHEMICAL**

## MARKETING NAME(S)

Listerine Total Care Mouthwash (contains notified chemical at < 0.05%)  
Menthyl succinate (INCI name)  
Physcool

## CAS NUMBER

77341-67-4

## CHEMICAL NAME

Butanedioic acid, 1-[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl] ester

## OTHER NAME(S)

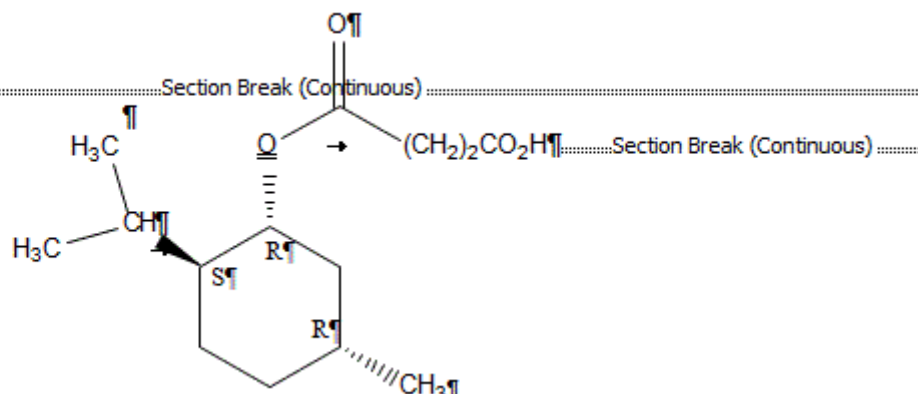
Butanedioic acid, mono[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl] ester (9CI)  
Butanedioic acid, mono[5-methyl-2-(1-methylethyl)cyclohexyl] ester, [1R-(1.alpha.,2.beta.,5.alpha.)]-  
Mono-menthyl succinate

MOLECULAR FORMULA  $C_{14}H_{24}O_4$ 

## MOLECULAR WEIGHT

256.3 Da

## STRUCTURAL FORMULA



## ANALYTICAL DATA

Reference IR spectra were provided.

**3. COMPOSITION**

DEGREE OF PURITY &gt; 99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (&gt;1% by weight) None

ADDITIVES/ADJUVANTS None

**4. PHYSICAL AND CHEMICAL PROPERTIES**

APPEARANCE AT 20°C AND 101.3 kPa: White powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	60°C	MSDS
Boiling Point	353°C at 101.3 kPa	Estimated (EPIWEB v 4.0)
Density	Not determined	Not isolated from aqueous solution
Vapour Pressure	2.3 x 10 <sup>-5</sup> kPa at 25°C	Estimated (EPIWEB v 4.0). Modified Antoine method using measured melting point of 60°C.
Water Solubility	44 mg/L at 20°C	Estimated
Hydrolysis as a Function of pH	Expected to be slow.	Estimated
Partition Coefficient (n-octanol/water)	log P <sub>ow</sub> = 4.1 at 20°C	Estimated
Adsorption/Desorption	log K <sub>oc</sub> = 2.1-2.4 at 20°C	Estimated
Dissociation Constant	pK <sub>a</sub> = 4.2	Analogue data (succinic acid)
Particle Size	Not determined	Not isolated from aqueous solution
Flash Point	Not determined	Not isolated from aqueous solution
Flammability	Not determined	Not isolated from aqueous solution
Autoignition Temperature	Not determined	Not expected to autoignite under normal conditions of use.
Explosive Properties	Not expected to be explosive	The structural formula contains no explosives.

**DISCUSSION OF PROPERTIES**

The notified chemical is predicted to be lipophilic and to have a low vapour pressure and low water solubility based on modelling (EPIWEB, 2009). While abiotic hydrolysis is expected to be slow, the notified chemical is likely to be rapidly hydrolysed by esterases under environmental conditions.

*Reactivity*

The notified chemical is expected to be stable under normal storage and handling conditions.

**5. INTRODUCTION AND USE INFORMATION****MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS**

The notified chemical will be imported as a component of finished personal care products at a concentration of < 0.05%.

**MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS**

<i>Year</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>Tonnes</i>	0.4	0.5	0.6	0.7	0.8

**PORT OF ENTRY**

Sydney

**TRANSPORTATION AND PACKAGING**

The notified chemical will be imported as a component of a finished cosmetic mouthwash in bottles up to 1L for retail sale and transported by road to the notifiers warehouse and then onto the retail store's central distribution centres.

**USE**

The notified chemical is a component of a flavour mixture used in a cosmetic mouthwash.

**OPERATION DESCRIPTION**

There will be no manufacture or reformulation of the notified chemical within Australia.

**6. HUMAN HEALTH IMPLICATIONS****6.1 Exposure assessment****6.1.1 Occupational exposure****EXPOSURE DETAILS**

Transport, storage and retail workers are not expected to be exposed to the notified chemical except in the unlikely event of an accident or spill.

**6.1.2 Public exposure**

The public will be exposed to the notified chemical at a concentration of up to 0.05% when using mouthwash products. Dermal and oral will therefore be the primary routes of exposure. Given the low vapour pressure of the notified chemical inhalation exposure is not expected. Accidental ocular exposure may occur, but is not expected to be significant.

Based on data reported by the Soap and Detergent Association (SDA) for European use, 8.5% of mouthwash is estimated to be ingested, equivalent to 70.8 mg/kg bw/day for a 60 kg adult using 10 g of the mouthwash product per use 5 times a day (SDA, 2005). Therefore exposure to the notified chemical at 0.05% is estimated as 0.04 mg/kg bw/day.

## 6.2. Human health effects assessment

No toxicity data were submitted.

The notified chemical is generally recognized as safe (GRAS) as a flavor ingredient by the expert panel of the Flavor and Extract Manufacturers Association (FEMA) (Smith et al, 1996).

The Joint FAO/WHO Expert Committee on Food Additives JECFA concluded that the substance does not present a safety concern at current levels of intake when used as a flavouring agent (1999a).

### *Toxicokinetics*

The notified chemical has a low molecular weight and is highly lipophilic; therefore penetration into the strata corneum would be expected. However, given its low water solubility (44 mg/L) the rate of transfer into the epidermis is expected to be low.

The notified chemical would be expected to hydrolyse in the body to (-)-menthol (CAS No. 2216-51-5) and butanedioic acid (CAS No. 110-15-6); the latter being endogenous to humans. Menthol is known to be readily absorbed by the oral route and largely eliminated as glucuronides. It has been reported that 70-80% is eliminated in urine and faeces within 48 hrs (JECFA, 1999a, 1999b).

### *Acute toxicity*

The notified chemical is expected to have a low acute oral toxicity based on a reported LD50 of > 5000 mg/kg on a study conducted on rats (JECFA, 1999a).

### *Repeated dose toxicity*

No repeat dose toxicity data was available for the notified chemical, however in a two year study conducted on groups of 50 rats of each sex fed the equivalent of 190 and 380 mg/kg bw/day of racemic menthol<sup>1</sup> in their diet, the NOEL was determined to be 380 mg/kg bw/day based on the absence of any treatment related effects (JECFA, 1999b).

### *Irritation and Sensitisation*

No irritation/sensitisation data was available for the notified chemical. The notified chemical may possess irritant properties as it contains a carboxylic acid group, a structural alert for skin irritants (Hulzebos, 2005) and eye irritants (Tsakovsha, 2007). Indeed, the notified chemical is listed on Safe Work Australia's hazardous substance information system (HSIS) as a severe eye irritant.

The notified chemical does not contain structural alerts for sensitisation and therefore is not expected to present as a sensitiser.

### *Genotoxicity*

No genotoxicity data was available for the notified chemical, however neither menthol<sup>1</sup> nor its metabolites were found to be genotoxic in a number of in vitro studies, including reverse mutation and chromosomal aberration tests, and in vivo tests (JECFA, 1999b).

### *Developmental toxicity*

No developmental toxicity data was available for the notified chemical, however in a study conducted on the expected metabolite of the notified chemical, (-)-menthol, no teratogenic effects were observed when tested at maximum doses of 190-430 mg/kg bw/day in mice, rats, hamsters and rabbits (JECFA, 1999b).

### *Carcinogenicity*

No carcinogenicity data was available for the notified chemical; however racemic menthol<sup>1</sup> was concluded to be not carcinogenic in studies conducted on rats and mice (JECFA, 1999b).

<sup>1</sup>Based on limited data, there is no indication of a difference in the metabolism and toxicity of (-)-menthol, the expected metabolite, and racemic menthol (JECFA, 1999b).

**Health hazard classification**

The notified chemical is listed on Safe Work Australia's hazardous substance information system (HSIS) as an eye irritant with the following risk phrase:

R41: Risk of serious damage to eyes

*Cutoffs:*

Conc  $\geq$  10%: Xi; R41

$\geq$  5%Conc < 10%: Xi; R36

Based on the available data the notified chemical is not classified as hazardous for other endpoints under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

**6.3. Human health risk characterisation****6.3.1. Occupational health and safety**

Given workers will only be exposed to low levels of the notified chemical in the event of an accident or spill, the risk to workers to the notified chemical is considered to be negligible.

**6.3.2. Public health**

The greatest risk of exposure to the notified chemical to the public will be by the oral route when using mouthwash products containing the notified chemical. The estimated exposure to the notified chemical in the mouthwash at up to 0.05% is 0.04 mg/kg bw/day. Given the NOEL (380 mg/kg bw/day) of the expected metabolite menthol is three orders of magnitude greater than the estimated exposure, the risk to the public is considered acceptable.

The risk of irritation effects are considered to be low/negligible based on the low concentration.

**7. ENVIRONMENTAL IMPLICATIONS****7.1 Environmental Exposure & Fate Assessment****7.1.1 Environmental Exposure****RELEASE OF CHEMICAL AT SITE**

The notified chemical will not be manufactured or reformulated in Australia. It is imported as a component of a finished cosmetic mouthwash in consumer containers.

There is unlikely to be any significant release to the environment, given the proposed relatively low level use for the product containing the notified chemical, the formulation and sealed packaging containers.

**RELEASE OF CHEMICAL FROM USE**

It is expected that the majority of the imported quantity of the notified chemical (estimated to be 99%) will be washed to the sewer as the chemical is intended for use in personal care products. This release will occur in a diffuse and widespread manner.

**RELEASE OF CHEMICAL FROM DISPOSAL**

It is estimated that 1% of the finished product goes into the garbage collection system as residues in empty containers. These residues may be sent to landfill with the containers, or washed to sewer when consumers rinse the containers before recycling.

**7.1.2 Environmental fate**

No environmental fate data were submitted. The notified chemical is expected to be easily hydrolysed in sewage treatment plants and the environment to menthol and succinic acid. These natural products can be expected to biodegrade easily. The notified chemical is not expected to bioaccumulate in fish because of the ease of enzymatic (esterase) hydrolysis in living organisms.

### 7.1.3 Predicted Environmental Concentration (PEC)

A PEC for the aquatic environment can be determined as tabulated below, assuming all the product containing the notified chemical is rinsed to sewer after use.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	800	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	800	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.19	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	21.374	million
Removal within STP	0%	
Daily effluent production:	4,275	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.51	µg/L
PEC - Ocean:	0.051	µg/L

## 7.2 Environmental effects assessment

No ecotoxicity data were submitted. The notifier has provided model estimates (EPIWEB, 2009) for the acute aquatic toxicity, as tabulated below.

	Duration	Predicted LC50/EC50
Fish	96 hour	21.06 mg/L
Fish (saltwater)	96 hour	25.43 mg/L
Daphnid	48 hour	32.88 mg/L
Green algae	96 hour	11.14 mg/L
Mysid shrimp	96 hour	9.89 mg/l

### 7.2.1 Predicted No-Effect Concentration

The PNEC can be determined as tabulated below by application of a thousand-fold assessment factor to the estimated acute toxicity to mysid shrimp.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Mysid 96 hour LC50	9.9	mg/L
Assessment Factor	1000	
PNEC:	9.9	µg/L

## 7.3 Environmental risk assessment

The risk quotients ( $Q = \text{PEC}/\text{PNEC}$ ) are tabulated below.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.51	9.9	0.052
Q - Ocean	0.051	9.9	0.0052

The notified chemical is not considered to pose a risk to the environment as the risk quotients are less than one.



## 8. CONCLUSIONS AND REGULATORY OBLIGATIONS

### Hazard classification

The notified chemical is listed on Safe Work Australia's hazardous substance information system (HSIS) as an eye irritant with the following risk phrase:

R41: Risk of serious damage to eyes

*Cutoffs:*

Conc  $\geq$  10%: Xi; R41

$\geq$  5%Conc < 10%: Xi; R36

Based on the available data the notified chemical is not classified as hazardous for other endpoints under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

and

As a comparison only, the classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

<i>Estimated mysid toxicity</i>	<i>Hazard category</i>	<i>Hazard statement</i>
96 hour LC50 = 9.9 mg/L	Acute 2	Toxic to aquatic life

As eye irritation data has not been cited, GHS classification for this endpoint has not been undertaken.

### Human health risk assessment

Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unacceptable risk to the health of workers.

When used in the proposed manner, the notified chemical is not considered to pose an unacceptable risk to public health.

### Environmental risk assessment

On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not considered to pose a risk to the environment.

### Recommendations

#### CONTROL MEASURES

##### Occupational Health and Safety

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified chemical as introduced, however, these should be selected on the basis of all ingredients in the formulation.

Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

- A copy of the MSDS should be easily accessible to employees.
- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

#### Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, collection and subsequent safe disposal.

### Regulatory Obligations

#### *Secondary Notification*

This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

- (1) Under Section 64(1) of the Act; if
  - the importation volume exceeds one tonne per annum notified chemical;or
- (2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from as a component of a finished cosmetic mouthwash at a concentration of < 0.05% , or is likely to change significantly;
  - the amount of chemical being introduced has increased from 0.8 tonnes per annum, or is likely to increase, significantly;
  - the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

#### *Material Safety Data Sheet*

The MSDS of the notified chemical and products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

### **BIBLIOGRAPHY**

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