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ISO/IEC 17025:2017 Testing Lab Report

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Project Number: 700025
Report Number: 700025-RP-01 (Rev E)

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Monroeville, PA 15146

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Subject: ISO 18562-3 Testing of the Philips Respironics Nirvana DreamStation, Moog Blower

Dear ,

This report includes the results from testing of the DreamStation that was tested according to ISO 18562-3. A toxicological risk assessment was completed based on the emission profiles detected during testing. The results of the 18562-3 testing and the corresponding risk assessment is contained within this report.

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1. Executive Summary

Project Description

Philips Respironics ("Philips") provided Plastics Services Network (PSN) with Nirvana DreamStation devices with a Moog Blower ("Nirvana DreamStation Moog") for testing and analysis. Testing of the CPAP was completed in accordance with ISO 18562-3. The emission profile was evaluated for VOCs and a toxicological risk assessment was completed including margins of safety for the emitted VOCs.

Testing and Results Summary

The test configuration and the overall results from the testing are contained within **Table 1**. The detailed results from the tests are contained within **Tables 2 and 3.**

Table 1: Testing Overview and Results Summary.

Testing Overview Summary		
Test Device	Nirvana DreamStation, Moog Blower CPAP, With Humidifier	
Serial Number	CPAP: J305193683C61 Humidifier: H305190119836	
VOC Testing Duration (Standard: ISO 18562-3)	168-hours	
Test Dates	03/17/2021 – 03/24/2021	
Emission Sample Collection Periods (ISO 18562-3)	T = 0-hours (initial operation) T = 24-hours T = 48-hours T = 72-hours T = 168-hours	
Flow Rate of Air Through Patient Device (VOC Emissions)	17 Liters/Minute	
Test Replicates	One device was tested	
Samples Received	March 2021	
Device/Test Settings	Humidifier off/non-operational for testing	
Ambient Test Temperature	35°C ± 2°C	
Test Operator(s)	DC, BH, KS, JV	
Test Location	5368 Kuhl Road Erie, PA 16510	
Testing Results Summary – Nirvana DreamStation Moog		
Number of VOC Substances Detected > 2.0 µg/m^3	43	
Risk Analysis	**MOS > 1.0**	**COPCs**
	36	7

Table 2: Philips Respironics Nirvana DreamStation Moog, Carbon Monoxide, Carbon Dioxide and Ozone Testing.

Philips Respironics Nirvana DreamStation Moog Carbon Monoxide, Carbon Dioxide, and Ozone Testing							
Substance Name	T = 0-hours Initial Operation (ppm)	T = 24-hours (ppm)	T = 48-hours (ppm)	T = 72-hours (ppm)	T = 168-hours (ppm)	Acceptance Standard (ppm)	Pass = MOS > 1.0
Carbon Monoxide (CO)	ND	ND	ND	ND	ND	9 [a]	Pass
Carbon Dioxide (CO_2)	630	551	583	366	498	1,000 [b]	Pass
Ozone (O_3)	0.10	ND	ND	ND	ND	0.05 [c]	Additional Analysis

ND = not detected
[a] National Ambient Air Quality Standard.
[b] Occupational Safety and Health Administration (OSHA 29 CFR 1910.124).
[c] Food and Drug Administration (FDA 21CFR801.415).

Table 3: Philips Respironics Nirvana DreamStation Moog Test Results, VOC Emissions.

Philips Respironics Nirvana DreamStation Moog ISO 18562-3 Testing							
CAS ID	NIST Compound Name	T = 0-hours VOC Concentration ($\mu g/m^3$)	T = 24-hours VOC Concentration ($\mu g/m^3$)	T = 48-hours VOC Concentration ($\mu g/m^3$)	T = 72-hours VOC Concentration ($\mu g/m^3$)	T = 168-hours VOC Concentration ($\mu g/m^3$)	Period of Maximum VOC Concentration (hours)
565-75-3	Pentane, 2,3,4-trimethyl- *	101.5	ND	ND	ND	ND	0
7154-79-2	Pentane, 2,2,3,3-tetramethyl- *	54.5	ND	ND	ND	ND	0
589-43-5	Hexane, 2,4-dimethyl- *	77.0	ND	ND	ND	ND	0
13475-78-0	Heptane, 5-ethyl-2-methyl- *	63.2	ND	ND	ND	ND	0
589-53-7	Heptane, 4-methyl- *	58.8	ND	ND	ND	ND	0
4032-86-4	Heptane, 3,3-dimethyl- *	54.5	59.7	ND	ND	ND	24
52670-34-5	Octane, 2,3,6,7-tetramethyl- *	154.1	ND	ND	ND	ND	0
2216-34-4	Octane, 4-methyl- *	62.0	ND	ND	ND	ND	0
1071-31-4	2,2,7,7-Tetramethyloctane *	52.4	ND	ND	ND	ND	0
111-84-2	Nonane +	19.4	9.5	ND	ND	ND	0
17302-28-2	Nonane, 2,6-dimethyl- *	80.8	ND	ND	ND	ND	0
124-18-5	Decane +	33.2	10.9	ND	ND	ND	0
13150-81-7	2,6-Dimethyldecane *	168.0	ND	ND	ND	ND	0
17312-66-2	Decane, 3-ethyl-3-methyl- *	49.5	ND	ND	ND	ND	0
1120-21-4	Undecane *	161.1	ND	ND	ND	ND	0
112-40-3	Dodecane *	81.4	ND	ND	ND	ND	0
67-63-0	Isopropyl Alcohol *	ND	857.1	ND	ND	ND	24
64-17-5	Ethanol *	50.2	44.1	ND	ND	ND	0
109-99-9	Tetrahydrofuran *	88.3	ND	ND	ND	ND	0
108-88-3	Toluene *	73.4	ND	ND	ND	ND	0
106-42-3	p-Xylene *	140.5	49.4	ND	ND	ND	0
100-41-4	Ethylbenzene *	65.2	ND	ND	ND	ND	0
98-82-8	Benzene, (1-methylethyl)- *	93.8	ND	ND	ND	ND	0
503-28-6	Diazene, dimethyl- *	1,254.0	ND	ND	ND	ND	0
141-78-6	Ethyl Acetate *	ND	85.3	ND	ND	ND	24
765-31-1	3-Methyl-1,2-diazirine *	387.6	313.7	ND	ND	ND	0
19549-87-2	2,4-Dimethyl-1-heptene *	142.7	ND	ND	ND	ND	0
15250-22-3	1-Octanol, 2,7-dimethyl- *	113.9	ND	ND	ND	ND	0
104-76-7	1-Hexanol, 2-ethyl- *	284.4	ND	ND	ND	ND	0
141-63-9	Pentasiloxane, dodecamethyl- *	368.1	64.8	ND	ND	ND	0
556-67-2	Cyclotetrasiloxane, octamethyl- +	128.7	ND	ND	ND	ND	0
541-05-9	Cyclotrisiloxane, hexamethyl- +	45.7	ND	ND	ND	ND	0

CAS ID	NIST Compound Name	T = 0-hours VOC Concentration (µg/m³)	T = 24-hours VOC Concentration (µg/m³)	T = 48-hours VOC Concentration (µg/m³)	T = 72-hours VOC Concentration (µg/m³)	T = 168-hours VOC Concentration (µg/m³)	Period of Maximum VOC Concentration (hours)
541-02-6	Cyclopentasiloxane, decamethyl- +	34.3	4.4	ND	ND	ND	0
629-82-3	Dioctyl ether +	330.2	75.6	ND	ND	ND	0
120-47-8	Ethylparaben *	195.7	ND	ND	ND	ND	0
NA	2-Hydroxymandelic acid, ethyl ester, di-TMS *	89.8	ND	ND	ND	ND	0
694-06-4	2,3,4,5-Tetrahydropyridazine *	ND	284.3	ND	ND	ND	24
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- *	489.1	224.8	ND	ND	ND	0
50-00-0	Formaldehyde *	59.0	15.9	0.6	0.4	ND	0
75-07-0	Acetaldehyde *	29.2	4.3	0.3	ND	ND	0
67-64-1	Acetone *	1,848.0	174.7	55.7	59.5	52.7	0
123-72-8	n-Butyraldehyde *	13.2	8.0	2.1	1.4	0.8	0
110-62-3	n-Valeraldehyde *	8.3	2.6	ND	ND	1.3	0

ND = not detected
* Quantification based on a multi-point standards curve.
+ Quantification based on toluene equivalence.

2. Introduction

Philips has a portfolio of breathing assistance devices, and related accessories that provide continuous or intermittent therapy for life sustaining and/or therapeutic needs, including continuous positive airway pressure (CPAP) devices. Medical devices that are indirect or direct patient contacting have specific guidance documentation that must be followed during the qualification process through submissions to the FDA. A requirement of such devices is to complete ISO 18562 testing. The broad umbrella of ISO 18562 covers the biocompatibility evaluation of breathing gas pathways in healthcare applications; ISO 18562-3 is specifically a test for emissions of volatile organic compounds (VOCs) and very volatile organic compounds (VVOCs).

VOCs can be deleterious to the health of patients, particularly those patients whose body mass is on the lower end of the patient spectrum (i.e., infants). The release of the ISO 18562 series of requirements has led to an increase in the amount of testing that must occur on finished devices. The benefit of testing the device is that it captures the device in the final assembled state in which the patient will encounter the device. The standard considers all manufacturing stages, processes, and materials of construction. In the event adhesives are used for bonding, those are effectively evaluated in the finished, as-manufactured state which is the intention of the standard.

PSN tested the Philips Nirvana DreamStation Moog (see **Figure 1**) in accordance with ISO 18562-3 for the emission and analysis of VOCs and VVOCs. PSN is an International Standards Organization (ISO) certified engineering services firm (ISO 9001:2015) that maintains an ISO/IEC 17025:2017 accredited testing laboratory. Testing was conducted under PSN's accreditation scope.

The CPAP was received by PSN in the as-manufactured state. The CPAP was tested in a manner that represented the final, finished, form (FFF) of the CPAP.

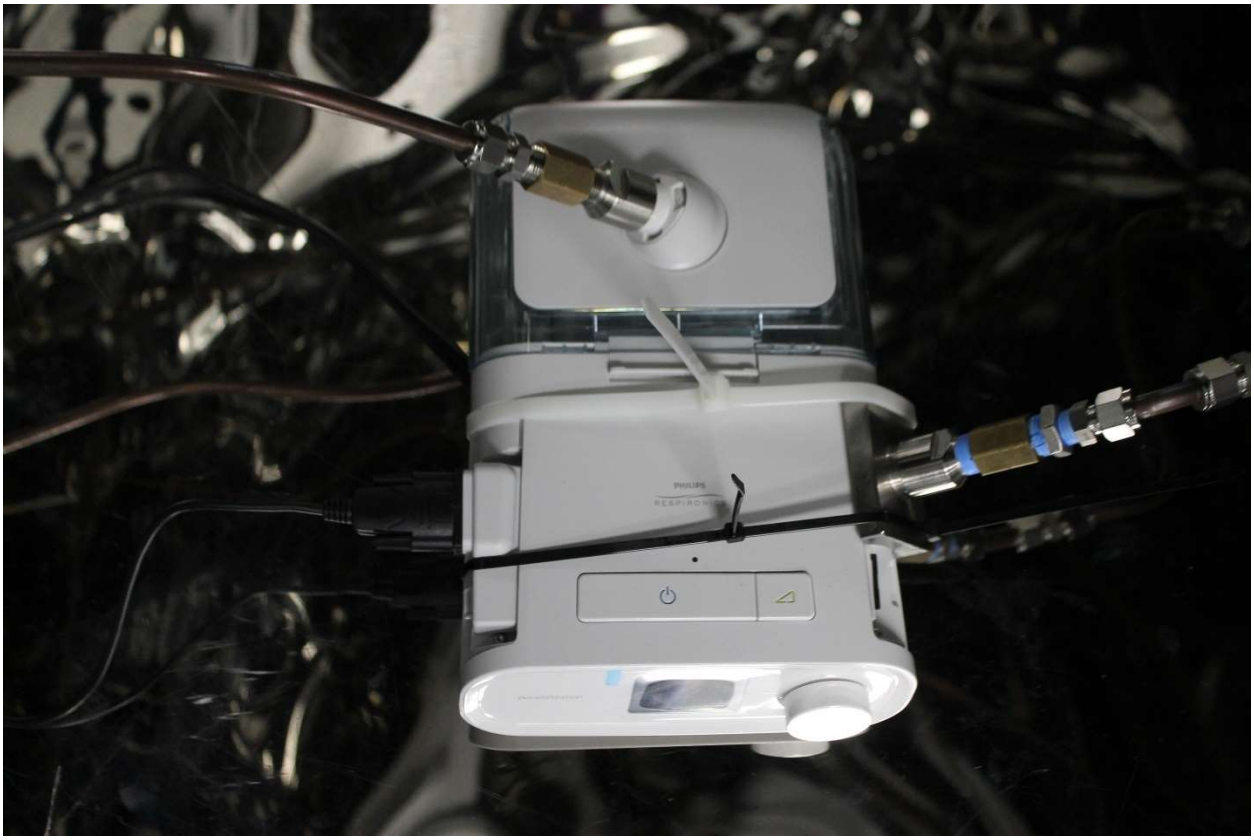


Figure 1: Philips Nirvana DreamStation Moog in the VOC Testing Chamber.

3. Testing Methods

PSN Test Setup

The core foundational principle maintained at PSN during the testing of medical components, products, and devices is to ensure patient safety through implementation of relevant controls and standards that isolate the output of interest to provide the best ratio of signal to noise while enhancing response variables and minimizing outside interference. The goal of ISO 18562 testing is to assess those VOCs that are present in, and are emitted by, devices connected to the breathing pathway and CPAP. VOCs are inherently present in the atmosphere that we breathe and exist within.

While laboratory environments may be more stable and sterile than the general spaces we exist within, sources of VOCs are present. Recognizing the criticality of eliminating outside sources of potentially confounding particulate content and VOCs, PSN conducts testing in sterile test chambers designed and manufactured with VOC free components; the chambers are built with VOC free stainless steel. The chambers are heated externally (i.e., no heating elements on the internal walls) to ensure no particulate or VOCs are introduced during testing. Temperature is maintained through use of a closed loop temperature controller. The test device was supplied with ultra-pure VOC free air from a Parker Balston

zero-air generator (SN: HPZA300000010A). This type of zero-air generator is designed to supply gas chromatography instrumentation with source gas; thus, the supply of test fluid (air) is purified to the highest extent possible and maintains a particulate filtration system. The CPAP gas pathway was connected directly to the sample collection ports exiting the chamber for emission collection with Silcosteel® that is coated with a SilcoTEK® coating to ensure that contamination (i.e., VOCs) from outside sources are not present and that VOCs are incapable of build-up on the internal surfaces of the test plumbing. The porting of the testing infrastructure directly interfaces with the collection apparatus to provide the ability to collect samples during the prescribed testing durations without introduction of outside interference. The test setup provides the ability to control the device and surrounding temperature absent of sources of particulate and VOC contamination. The only items within the test chamber are the test device (CPAP), and the zero-air inlet and outlet plumbing for the test air. **Figure 1** highlights the test construct in which the device is connected directly to the zero-air inlet and outlet of the chamber. Testing occurred for the Philips Nirvana DreamStation Moog device in chamber serial number C0001.

Testing Parameters
The Parker-Balston zero-air generator fed the test device at a flow rate of 17.0 L/min. The chamber was held at 35°C ± 2°C during the 168-hour testing duration. VOC samples were collected over 1-hour durations at each sample collection interval according to TO-17 and TO-11A.

VOC Collection
ISO 18562-3 testing occurs according to TO-17 and TO-11A. Air samples were collected in thermal desorption tubes for TO-17 and DNPH cartridges for TO-11A. Standard TO-17 sample collection occurs for C2/C3 through C30 collecting 17 liters of air at each test point. Aldehydes and ketones (TO-11A) were sampled such that 45 liters of air was collected during each collection period.

Thermal desorption tubes from Markes International, product ID #C3-AAXX-5266 were used for the TO-17 tests. The aldehyde and ketone samples are collected utilizing Supelco/Sigma Aldrich BPE-DNPH cartridges for TO-11A. Fresh, conditioned (never used) tubes are used for each sample collection point. Flow control for the test is maintained by setting the zero-air generator to supply constant flow to the CPAP at 17.0 L/min.

VOC Testing
Carbon monoxide (CO), carbon dioxide (CO2), and ozone (O3) are measured using Forensics Detectors model FD-600A and FD-90A-low-O3 detectors.

Collected VOC samples were tested utilizing a Perkin Elmer Gas-Chromatography/Mass-Spectrometer (GC-MS) (Perkin Elmer 690 GC/ SQ8T MS, Thermal Desorber SN: TD650S1906184, Gas Chromatograph SN:690S20061802, Mass Spectrometer SN: 648N20010704VR).

Collected aldehyde samples from the sample collection points were tested utilizing a Perkin Elmer High-performance Liquid Chromatograph (HPLC) (Flexar Modular HPLC, Solvent Manager SN: 260N19060505Q, Autosampler SN: 293H9041201A, PDA SN: 295N19050801B).

The collected VOCs are qualitatively and quantitatively screened using gas chromatography with mass spectrometric detection (GC-MS) according to ISO 16000-6 for VOCs and is complemented with high pressure liquid chromatography (HPLC) according to ISO 16000-3, ASTM D5197 and USEPA method TO-11A for low molecular weight aldehydes and ketones. Individual VOCs emitted from the Philips CPAP were identified using the PSN environmental and NIST traceable spectral databases which includes over 306,600 validated compounds. Those substances with high spectral quality and with readily available traceable standards are also run as known calibration curves to enhance the quantification data. Standard quantification of those standards occurs and those VOCs that have been quantified based on custom standards analysis are highlighted in the output section of this report; these individual VOCs were quantified using the multipoint calibration standards. All other unique substances detected were quantified against toluene as a surrogate and are labeled as such.

Following the guidance of ISO 18562-1 clause 5.3 and clause 7, detected VOCs are identified and reported at or above 2.0 µg/m^3. This gives a total dose-to-patient for an adult (who breathes 20.0 m^3/d) of 40 µg, which represents the increase in excess cancer risk of 1 in 2.7 x 10^{-4} for long term exposure per ISO 18562-1 clause 7.4. The scaling of breathing volumes according to patient weight was completed in accordance with ISO 18562-1 clause 6.2.

4. Toxicological Risk Assessment Strategy

Biocompatibility Assessment

ISO 18562-3 testing requires the identification and quantification of VOCs that are emitted as a function of standard operation of a medical device and/or component of interest. Biocompatibility assessments are critical to ensure the device is safe for use. Assessment is a two-step process:

a) Identify and quantify those substances which are emitted as VOCs
b) Complete a toxicological risk assessment

Toxicological Risk Assessments (TRA)

The objective of a toxicological risk assessment (TRA) is to evaluate the potential health risks associated with exposure to leachable impurities, contaminants, or other residues in a medical device. The chemical characterization of those impurities, contaminants, residues – and in the case of ISO 18562 – VOCs and aldehydes/ketones are critical for patient safety. It is the intention of these risk assessments to make a determination as to whether the release of such chemicals during the use of the medical device may represent a toxicological risk that is unacceptable.

Toxicological Risk Assessment: Background

Risk assessments for VOCs entail identification of the VOC(s) that are present within a device that could pose health hazards. It is critical to quantify the concentrations at which they are present. This is effectively completed through the ISO 18562-3 testing.

The second aspect of the initial risk assessment process is evaluating the substances of concern, in this case the VOCs, for their toxicological behaviors. Identification of thresholds of concern for each substance and the completion of mathematical models is used to identify/provide a quantified risk. This step may include an assessment of variations in response – for example, differences in susceptibility between infant

and elderly populations, particularly when high risk substances and/or high-risk concentrations are detected.

Risk Assessment Stage 1: Margin of Safety (MOS) from Established Air Thresholds

The relationship between a hazard and the corresponding potential for exposure is what classically defines risk. Toxicological risk assessments determine, at the fundamental level, whether a product poses a potential risk for the toxicological endpoints measured. The initial data used within the MOS calculations is spread across multiple agencies that are both national and internationally available and recognized. The European Chemical Agency (ECHA) database, which has largely been responsible for the REACH regulation (Registration, Evaluation, Authorization, and Restriction of Chemicals), is used as the primary source for as many substances as possible. This is one of the largest databases that maintains coherent guidelines which are well-sourced, consistent, and contain uniform guidance.

An initial margin of safety (MOS) screening was conducted for each VOC based on the worst case published *Derived No Effect Level (DNEL)* for the *inhalation hazards* in which *systemic effects* for *long term exposure* for the *general population* have been issued based on the maximum measured VOC from the test device (see **Equation 1**). VOCs that maintain a MOS of less than 1.0 or those VOCs that have been classified as a carcinogen or reproductive toxicant are considered to be chemicals of potential concern (COPCs).

(1) $$MOS = \frac{Lowest\ health{-}based\ air\ threshold\ (\frac{\mu g}{m^3})}{Maximum\ measured\ VOC\ Concentration\ (\frac{\mu g}{m^3})}$$

Risk Assessment Stage 2: Deriving Tolerable Consumer Dose and Tolerable Exposure Limits

COPCs were identified in the Stage 1 calculations. The risk-based approaches of ISO 18562-1 and ISO 10993-17 allows for the evaluation of COPCs by integrating available hazard information for each COPC and exposure data based on patient exposure. Evaluation of the COPCs occurs through:

- Development of tolerable exposure dose for each COPC
- Calculation of patient inhalation dose for each COPC

This allows for the MOS to be calculated (**Equation 2**). The target MOS is greater than 1.0 and when it is achieved no further work on the hazard is required and the decision shall be documented.

(2) $$MOS = \frac{Tolerable\ daily\ exposure\ (\frac{\mu g}{day})}{Patient\ daily\ dose\ (\frac{\mu g}{day})}$$

The tolerable exposure (TE) doses were based on published health based tolerable exposure limits or based on threshold of toxicological concern (TTC) from ISO 10993-17 and ISO 18562-1 guidance. The average daily COPC dose the patient receives during use of the device depends on the percentage of device air comprising the patient airstream flow, the daily volume of air inhaled by the patient through the device (in m^3/day), and the concentration of the COPC measured from testing of the device (in $\mu g/m^3$). The patient-based calculations within ISO 18562-1 are based on an adult patient (70 kg); clause 6.2 provides guidance for the adjustment of body weight for various patient populations. For a device in which permanent contact is designed (i.e., greater than or equal to 30 days of use) a TTC value of

360 µg/day is used for the first 24-hours of exposure in which a VOC is not detected thereafter. Those substances in which unknown toxicity exists have a TTC value of 40 µg/day according to ISO 18562-1.

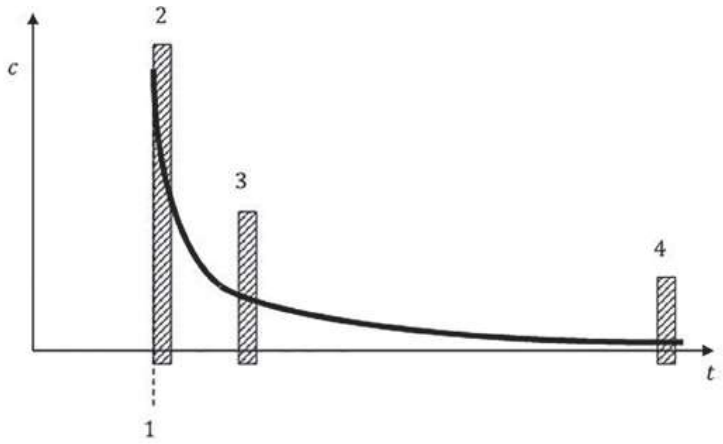
Analysis of chronic exposure risk requires the calculation of the time weighted averages (TWA) of the COPCs and those substances that could pose additional risk. Specifically, for all non-carcinogenic COPCs, a TWA concentration is calculated over the first 30 days of use based on the sum of the COPC sample period durations multiplied by the concentration of the COPC measured during the previous sample divided by the total exposure time. The calculation for the TWA concentration is conducted with the assumption of a 30-day sampling period in which the sum of the sampling durations is combined with the measured VOC concentrations (see **Equation 3** where C_x is the measured VOC concentration and t_x is the estimated duration of exposure at the sampling period C_x in hours). The conservativeness of this calculation is rooted in the assumption that the concentration of the measured VOC remains constant over the 30-day duration. The TWA calculation generally analyzes the concentrations of emitted VOCs detected during initial operation, at 24-hours of operation, 48-hours of operation, at 72-hours of operation, at 168-hours of operation (c_1, c_2, c_3, c_4, c_5) where t_1 = 24 hours, t_2 = 24 hours, t_3 = 24 hours, t_4 = 96 hours, and t_5 = 552 hours. The calculation assumes that the quantified emission of VOCs from the initial point to the final point of a time period (i.e., from the initial reading at t = 0 hours to t = 24 hours) is uniform and constant. This provides a degree of conservatism in the calculation.

(3) $$TWA = \frac{t_1c_1+t_2c_2+t_3c_3+t_4c_4+t_5c_5}{t_1+t_2+t_3+t_4+t_5}$$

COPCs with chronic exposure risks such as cancer where the toxicity thresholds are described in terms of lifetime probabilities, the exposure doses are typically calculated as lifetime average daily doses (LADDs). The relevant period for carcinogenic exposure is not based on a single daily exposure concentration but on the average of the daily exposure concentrations that occur over a consumer's lifetime (US EPA 1992; 2005). A daily inhalation exposure dose is converted to a LADD based on the number of days a year a consumer is exposed averaged over the consumer's expected lifetime. The duration of usage of the CPAP is up to 24-hours per day for a 10-year life duration. Therefore, lifetime average daily doses for the carcinogens were developed assuming a patient will inhale the TWA carcinogenic COPC gas concentration daily for 10 years averaged over a 70-year lifetime (see **Equation 4**) where C is the average daily concentration of COPCs (30-day TWA, µg/m^3) IR is the inhalation rate (m^3/day based on 20 m^3/day for a 70 kg adult, ET is the exposure time (hours/day, 24-hour exposure), EF is the exposure frequency (365-days/year), ED is the exposure duration (10-years), B is the bioavailability (B = 1.0), BW is the patient body weight (kg) and LT is the patient lifetime (70-years).

(4) $$LADD = \frac{C*IR*ET*EF*ED*B}{BW*LT}$$

Patient safety is critical in the calculation of the TWA that is used in risk assessment calculations such as MOS. Therefore, the TWA calculations are expected to be conservative as a reduction in concentration of emitted VOCs generally occurs after the initial sampling periods. The concentrations of VOC emissions generally decrease during a 168-hour sampling period (see **Figure 2**). Chronic exposures to maximum VOC levels over prolonged durations generally does not occur.



Key

c	concentration
t	time
1	start of test
2	sample at start
3	sample at 24 h
4	sample at end of use or at steady state

Figure 2: Typical VOC Decay Curve (Concentration vs. Time) per Figure 2 of ISO 18562-3.

5. Risk Assessment Data, Stage 1

Forty-three (43) VOCs were detected in the Philips Nirvana DreamStation Moog emission profile (see **Table 4).** Established health-based thresholds exist for thirty-eight (38) of the forty-three (43) substances detected within the emission profile. MOS calculations were completed. Formaldehyde and acetaldehyde were observed in the emission profile; both are a chronic exposure risk for cancer and are classified as COPCs. Additional analysis was conducted. Five substances lacked health-based thresholds and are classified as COPCs; additional analysis was conducted. Seven (7) total substances were identified as COPCs. The remaining thirty-six (36) VOCs had calculated MOS of greater than 1.0; additional analysis for these substances was unnecessary.

Table 4: MOS Calculations, Philips Nirvana DreamStation Moog.

CAS ID	NIST Compound Name	Maximum Concentration VOC Testing (µg/m³)	Sampling Period of Maximum Concentration (hours)	Health Based Threshold (µg/m³)	MOS	Pass/Fail (Pass = MOS > 1.0)
565-75-3	Pentane, 2,3,4-trimethyl-	101.5	0	643,000 [a]	6,335.0	Pass
7154-79-2	Pentane, 2,2,3,3-tetramethyl-	54.5	0	643,000 [a]	11,798.2	Pass
589-43-5	Hexane, 2,4-dimethyl-	77.0	0	1,131,000 [b]	14,688.3	Pass
13475-78-0	Heptane, 5-ethyl-2-methyl-	63.2	0	447,000 [c]	7,072.8	Pass
589-53-7	Heptane, 4-methyl-	58.8	0	447,000 [c]	7,602.0	Pass
4032-86-4	Heptane, 3,3-dimethyl	54.5	24	447,000 [c]	7,487.4	Pass
52670-34-5	Octane, 2,3,6,7-tetramethyl-	154.1	0	608,000 [a]	3,945.5	Pass
2216-34-4	Octane, 4-methyl-	62.0	0	608,000 [a]	9,806.5	Pass
1071-31-4	2,2,7,7-Tetramethyloctane	52.4	0	608,000 [a]	11,603.1	Pass
111-84-2	Nonane	19.4	0	185,000 [d]	9,536.1	Pass
17302-28-2	Nonane, 2,6-dimethyl-	80.8	0	185,000 [d]	2,289.6	Pass
	Total Hydrocarbons ≤ C9	*778.2*	0	*185,000 [d]*	*236.2*	*Pass*
124-18-5	Decane	33.2	0	12,000 [e]	361.4	Pass
13150-81-7	2,6-Dimethyldecane	168.0	0	12,000 [e]	71.4	Pass
17312-66-2	Decane, 3-ethyl-3-methyl-	49.5	0	12,000 [e]	242.4	Pass
1120-21-4	Undecane	161.1	0	12,000 [e]	74.5	Pass
112-40-3	Dodecane	81.4	24	12,000 [e]	147.4	Pass
	Total Hydrocarbons ≥C10 ≤ C18	*493.2*	0	*12,000 [e]*	*24.3*	*Pass*
67-63-0	Isopropyl Alcohol	857.1	0	980,000 [f]	1,143.4	Pass
64-17-5	Ethanol	50.2	0	114,000 [a]	2,270.9	Pass
109-99-9	Tetrahydrofuran	88.3	0	13,000 [a]	147.2	Pass
108-88-3	Toluene	73.4	0	56,500 [a]	769.8	Pass
106-42-3	p-Xylene	140.5	0	65,300 [a]	464.8	Pass
100-41-4	Ethylbenzene	65.2	0	4,420 [g]	67.8	Pass
98-82-8	Benzene, (1-methylethyl)-	93.8	24	16,600 [a]	177.0	Pass
503-28-6	Diazene, dimethyl-	1,254.0	0	NA	NA	Additional Analysis
141-78-6	Ethyl Acetate	85.3	0	367,000 [a]	4,302.5	Pass
765-31-1	3-Methyl-1,2-diazirine	387.6	0	NA	NA	Additional Analysis
19549-87-2	2,4-Dimethyl-1-heptene	142.7	0	10,200 [h]	71.5	Pass
15250-22-3	1-Octanol, 2,7-dimethyl-	113.9	0	435 [i]	3.8	Pass

CAS ID	NIST Compound Name	Maximum Concentration VOC Testing (µg/m³)	Sampling Period of Maximum Concentration (hours)	Health Based Threshold (µg/m³)	MOS	Pass/Fail (Pass = MOS > 1.0)
104-76-7	1-Hexanol, 2-ethyl-	284.4	0	24,500 [a]	86.1	Pass
141-63-9	Pentasiloxane, dodecamethyl-	368.1	0	25,000 [a]	67.9	Pass
556-67-2	Cyclotetrasiloxane, octamethyl-	128.7	0	13,000 [a]	101.0	Pass
541-05-9	Cyclotrisiloxane, hexamethyl-	45.7	0	640 [j]	14.0	Pass
541-02-6	Cyclopentasiloxane, decamethyl-	34.3	0	17,300 [a]	504.4	Pass
629-82-3	Dioctyl ether	330.2	0	87,000 [a]	263.5	Pass
120-47-8	Ethylparaben	195.7	0	52,170 [a]	266.6	Pass
NA	2-Hydroxymandelic acid, ethyl ester, di-TMS	89.8	0	NA	NA	Additional Analysis
694-06-4	2,3,4,5-Tetrahydropyridazine	284.3	24	NA	NA	Additional Analysis
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)-	489.1	0	NA	NA	Additional Analysis
50-00-0	Formaldehyde	59.0	0	9 [k]	0.2	Additional Analysis
75-07-0	Acetaldehyde	29.2	0	9 [l]	0.3	Additional Analysis
67-64-1	Acetone	1,848.0	0	447,000 [a]	241.9	Pass
123-72-8	n-Butyraldehyde	13.2	0	750 [m]	56.8	Pass
110-62-3	n-Valeraldehyde	8.3	0	1,760 [n]	212.0	Pass

[a] Available ECHA General Population DNEL data for inhalation hazards for systemic effects for long-term exposure.
[b] Available ECHA General Population DNEL data for inhalation hazards for systemic effects for long-term exposure, C6, iso-alkanes.
[c] Available ECHA General Population DNEL data for inhalation hazards for systemic effects for long-term exposure, C7 n-alkanes, iso-alkanes, cyclics.
[d] Available ECHA General Population DNEL data for inhalation hazards for systemic effects for long-term exposure, hydrocarbons, C9-C10, n-alkanes, isoalkanes, cyclics, <2% aromatics.
[e] 1% of the occupational exposure limit for C10 to C15 https://doi.org/10.3109/10408444.2015.1016216.
[f] Isopropyl alcohol TWA PEL 980 mg/m3 09 2006 US-California OELs.
[g] 1% of the ECHA DMEL for Workers – hazards via inhalation.
[h] ECHA General Population DNEL data for inhalation hazards for systemic effects for long-term exposure, C9-C11, C10 rich alkenes; no hazard identified for < C9 alkenes.
[i] 1% of the available ECHA General Population DNEL data for inhalation hazards for systemic effects for long-term exposure for 1-octanol.
[j] 1% of the ECHA DNEL for Workers – hazards via inhalation.
[k] OEHHA ChREL.
[l] US EPA IRIS.
[m] 1% of the OARS WEEL 8-hr time-weighted average
[n] 1% of the ACGIH TLV (USA) for occupational exposure.

6. Risk Assessment Data, Stage 2

Seven (7) substances were classified as COPCs. Formaldehyde and acetaldehyde present chronic exposure risks for carcinogenicity. Diazene, dimethyl-, 3-Methyl-1,2-diazirine, 2-Hydroxymandelic acid, ethyl ester, di-TMS, and 2,3,4,5-Tetrahydropyridazine, and Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- lack health-based thresholds. These seven substances were analyzed for two patient cases:

a) 70 kg Adult with a breathing volume of 20.0 m^3/day
b) 30 kg patient with a breathing volume of 8.6 m^3/day

The MOS calculations (see **Tables 5 and 6**) used tolerable safe daily dose information and the corresponding daily inhalation exposure doses in order to further assess risk for the patient populations.

The tolerable safe doses were based on established limits for formaldehyde and acetaldehyde and the unknown substances were evaluated using default thresholds of toxicological concern (TTC) from ISO 18562-1. Formaldehyde and acetaldehyde maintained a MOS for both patient populations of greater than 1.0 when using the LADD calculation which is appropriate for chronic exposure risk. Additional analysis was unnecessary. The LADD calculations used the daily dose calculated based on 10-years of continuous exposure to the TWA over a 70-year lifetime to effectively assess risk for the chronic exposure risk COPCs. Additional analysis for formaldehyde and acetaldehyde was unnecessary.

One of the substances, 2-Hydroxymandelic acid, ethyl ester, di-TMS, that lacked health-based thresholds maintained a MOS of greater than 1.0 when considering the 30-day TWA and the corresponding daily exposure dose to both patient populations. Additional analysis was unnecessary.

The remaining four substances that lacked health-based thresholds (Diazene, dimethyl-, 3-Methyl-1,2-diazirine, and 2,3,4,5-Tetrahydropyridazine) had calculated MOS values of less than 1.0 when considering the 30-day TWA and the corresponding daily exposure dose for both patient populations. Additional analysis for these substances was necessary. These substances are considered compounds of concern (COCs) and require additional hazard characterization.

Table 5: COPC MOS Calculations for a 70 kg Patient, Nirvana DreamStation Moog.

CAS Number	Substance	30-Day TWA (µg/m³)	Daily Dose 70 kg Patient (µg/day)	Daily Tolerable Exposure Dose (µg/day)	MOS	Pass/Fail (Pass = MOS > 1.0)
503-28-6	Diazene, dimethyl-	41.8	836.0 [a]	360.0 [b]	0.4	Additional Analysis
765-31-1	3-Methyl-1,2-diazirine	23.4	258.4 [a]	120.0 [c]	0.3	Additional Analysis
NA	2-Hydroxymandelic acid, ethyl ester, di-TMS	3.0	59.9 [a]	360.0 [b]	6.0	Pass
694-06-4	2,3,4,5-Tetrahydropyridazine	9.5	189.5 [a]	120.0 [c]	0.6	Additional Analysis
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)-	23.8	475.9 [a]	120.0 [c]	0.3	Additional Analysis
50-00-0	Formaldehyde	2.6	7.3 [d]	40.0 [e]	5.4	Pass
75-07-0	Acetaldehyde	1.1	3.2 [d]	90.0 [e]	28.0	Pass

[a] Daily dose calculated based on 30-day TWA and an adult breathing volume of 20 m³/day.
[b] Toxicity threshold of concern (TTC) of 360 µg/day is adult specific for COPCs present only in the initial sample collection period per ISO 18562-1.
[c] Toxicity threshold of concern (TTC) of 120 µg/day is adult specific for COPCs present in the second 24-hr sample collection period per ISO 18562-1.
[d] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime.
[e] Tolerable dose based on OEHHA Safe Harbor value.

Table 6: COPC MOS Calculations for a 30 kg Patient, Nirvana DreamStation Moog.

CAS Number	Substance	30-Day TWA (µg/m³)	Daily Dose 30 kg Patient (µg/day)	Daily Tolerable Exposure Dose (µg/day)	MOS	Pass/Fail (Pass = MOS > 1.0)
503-28-6	Diazene, dimethyl-	41.8	359.5 [a]	154.3 [b]	0.4	Additional Analysis
765-31-1	3-Methyl-1,2-diazirine	23.4	201.0 [a]	51.4 [c]	0.3	Additional Analysis
NA	2-Hydroxymandelic acid, ethyl ester, di-TMS	3.0	25.7 [a]	154.3 [b]	6.0	Pass
694-06-4	2,3,4,5-Tetrahydropyridazine	9.5	81.5 [a]	51.4 [c]	0.6	Additional Analysis
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)-	23.8	204.7 [a]	51.4 [c]	0.3	Additional Analysis
50-00-0	Formaldehyde	2.6	3.2 [d]	40.0 [e]	28.0	Pass
75-07-0	Acetaldehyde	1.1	1.4 [d]	90.0 [e]	65.0	Pass

[a] Daily dose calculated based on 30-day TWA and a breathing volume of 8.6 m³/day for a 30 kg patient.
[b] Toxicity threshold of concern (TTC) of 154.3 represents a de-rating of the 360 µg/day adult specific for COPCs present only in the initial sample collection period per ISO 18562-1 (360 µg/day x 30 kg/70 kg).
[c] Toxicity threshold of concern (TTC) of 51.4 µg/day represents a de-rating of the 120 µg/day adult specific for COPCs present in the second 24-hr sample collection period per ISO 18562-1 (120 µg/day x 30 kg/70 kg).
[d] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime.
[e] Tolerable dose based on OEHHA Safe Harbor value.

7. Risk Assessment Stage 3: Compounds of Concern (COC)

The MOS for all COPCs was greater than 1.0 except for:

- Diazene, dimethyl-,
- 3-Methyl-1,2-diazirine, and
- 2,3,4,5-Tetrahydropyridazine
- Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)-

These substances are considered COCs and additional hazard characterization was completed. In order to conduct an additional screen on the compounds of concern, endpoints such as overall toxicity, genotoxicity, and carcinogenicity were explored *in silic*o. Software included JRC (Joint Research Centre) commissioned, toxicological decision tree and database software ToxTree (v 3.1.0.1851 available at http://toxtree.sourceforge.net/).[1] ToxTree runs through a series of decision trees based upon the internationally accepted Cramer Classification Scheme, along with data sourced from various mutagenicity and carcinogenicity databases.[2] Structural screening on the compounds was conducted if applicable utilizing Derek Nexus v.2.3.1 Build 84 Nov 2020 software which can aid in determining mutagenic, sensitizing, and non-cancer toxicity based upon Quantitative Structure Activity Relationships (QSAR). All predictions were set to "plausible" as a threshold level, which yields predictive, possible, toxicity outcomes that are not always definitive. This was done to be conservative and protect all patient populations that utilize the DreamStation device. The quantitative structure-activity relationship (QSAR) is utilized in toxicology in order to predict the toxicological effects of unknown or data poor chemicals,

[1] Patlewicz, G., Jeliazkova, N., Safford, R. J., Worth, A. P. & Aleksiev, B. An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. *SAR and QSAR in Environmental Research* **19**, 495–524 (2008).
[2] Cramer, G. M., Ford, R. A. & Hall, R. L. Estimation of toxic hazard—A decision tree approach. *Food and Cosmetics Toxicology* **16**, 255–276 (1976).

and QSAR modeling has emerged as a fundamental tool in predictive toxicology.[3,4] Chemicals which were analyzed through these methods are listed in the appendix of this document with outputs from the various software if applicable. All output reports are included in the Appendix of this report.

Hazard Identification

Dimethyl diazene (CAS Number: 503-28-6)

This compound is also known as azomethane with no specific pre-clinical toxicological data available in scientific literature, nor a known daily permissible daily exposure limit. The oxide derivative of this compound, azoxymethane (CAS Number 25843-45-2) is a potent carcinogen.[5] It is feasible that both azomethane and its oxidized form (azoxymethane) would be present during device operation, as gases flow through and interact with the device. In order to be inclusive of the worst-case clinical scenario, as well as protective of all patient populations that the Nirvana DreamStation device is intended for (≥30 kg), both azomethane and azoxymethane toxicological limits were utilized for the MOS calculations. The previous tolerable intake levels utilized for the preceeding compound of potential concern (COPC) screening was 360 ug/day during the first 24 hours of exposure, adjusted for a 30 kg patient, per ISO 18562-3:2017. When recalculated with the ICH M7 guideline of 1.5 µg/day for long-term exposure to a potential mutagenic or carcinogenic analyte, the margin of safety is still below 1 for both exposure scenarios which include only 8 hours of exposure, indicating a potential hazard. A re-calculation of the lifetime average daily dose for the 30 kg patient population using the 8-hour/24-hour exposure window to capture a more clinically relevant exposure time with use of the device still results in MOS values of less than 1.0 for both 30 and 70 kg patient populations. This confirms dimethyl diazine and its oxidized derivative as a COC.

[3] Benigni, R. & Bossa, C. Flexible use of QSAR models in predictive toxicology: a case study on aromatic amines. *Environ. Mol. Mutagen.* **53**, 62–69 (2012).
[4] Benigni, R. Predictive toxicology today: the transition from biological knowledge to practicable models. *Expert Opinion on Drug Metabolism & Toxicology* **12**, 989–992 (2016).
[5] Waly, M.I., Al-Rawahi, A.S., Al Riyami, M. *et al.* Amelioration of azoxymethane induced-carcinogenesis by reducing oxidative stress in rat colon by natural extracts. *BMC Complement Altern Med* **14,** 60 (2014). https://doi.org/10.1186/1472-6882-14-60.

Table 7: Additional Analysis for Diazine, Dimethyl-, Nirvana DreamStation Moog.

CAS Number	Substance	30-Day TWA (µg/m³)	Patient Size (kg)	Daily Dose (µg/day)	Daily Tolerable Exposure Dose (µg/day)	MOS	Pass/Fail (Pass = MOS > 1.0)
503-28-6	Diazene, dimethyl-*	41.8	30	359.5 [a]	1.5 [d]	0.004	Additional analysis
503-28-6	Diazene, dimethyl-*	41.8	30	119.8 [b]	1.5 [d]	0.012	Additional analysis
503-28-6	Diazene, dimethyl-*	41.8	30	51.4 [c]	1.5 [d]	0.029	Additional analysis
503-28-6	Diazene, dimethyl-*	41.8	30	17.1 [e]	1.5 [d]	0.088	Fail
503-28-6	Diazene, dimethyl-*	41.8	70	39.8 [e]	1.5 [d]	0.952	Fail

*Both dimethyl diazene (azomethane) and dimethyl-1-oxide diazene (azoxymethane) were considered substances for this hazard analysis.

[a] Daily dose calculated based on 30-day TWA and a 30 kg breathing volume of 8.6 m³/day.
[b] Daily dose calucated based on 30-day TWA and a 30 kg breathing volume adjusted for 8 hours/24 hour exposure per day.
[c] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime.
[d] Tolerable Exposure based on ICH M7 mutagenic/carcinogenic 1.5 µg/day limit for long-term exposure, inclusive of all patient weights.
[e] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime adjusted daily dose for 8-hours out of 24-hour exposure per day.

3-methyl-1,2-diazirine (CAS Number: 765-31-1)

This compound is also known as 3-methyl-3H-diazirine with neither specific pre-clinical toxicological data available in scientific literature nor a known daily permissible daily exposure limit. A QSAR analysis with the Derek Nexus predictive software revealed no specific structural alerts for mutagenicity, sensitization, or other toxicological endpoints of note. An analysis with modified Cramer class rules based on the absence of mutagenic/genotoxic alerts from Derek Nexus with the ToxTree software resulted in the label of a Class III compound for 3-methyl-1,2-diazrine. The permissible exposure limit is changed to 1.5 ug/kg bw/day, resulting in 45 µg and 105 µg respectiviely for the 30 and 70 kg patient populations. The previous tolerable intake levels utilized for the preceeding compound of potential concern (COPC) screening was 360 ug/day during the first 24 hours of exposure, adjusted for a 30 kg patient, per ISO 18562-3:2017. When recalculated with the Cramer Class III designation, the margin of safety is still below 1.0 for both exposure scenarios which include only 8 hours of exposure, indicating a potential hazard. A re-calculation of the lifetime average daily dose based on the TWA for the 30 kg patient population does result in a MOS > 1.0. The same is true for an adjusted lifetime average daily dose of 66.8 µg/day for a 70 kg patient, also resulting in a MOS > 1.0. If the LADD daily dose calculations were further adjusted to incorporate only 8 hours of exposure into the calculation, the MOS value would increase to 4.7 as opposed to 1.6, which is only just above the 1.0 threshold for continuous (24-hour) exposure.

Table 8: Additional Analysis for 3-Methyl-1,2-Diazirine, Nirvana DreamStation Moog.

CAS Number	Substance	30-Day TWA (µg/m³)	Patient Size (kg)	Daily Dose (µg/day)	Daily Tolerable Exposure Dose (µg/day)	MOS	Pass/Fail (Pass = MOS > 1.0)
765-31-1	3-methyl-1,2-diazirine	23.4	30	201.0 [a]	45.0 [d]	0.2	Additional analysis
765-31-1	3-methyl-1,2-diazirine	23.4	30	67.0 [b]	45.0 [d]	0.7	Additional analysis
765-31-1	3-methyl-1,2-diazirine	23.4	30	28.7 [c]	45.0 [d]	1.6	Pass
765-31-1	3-methyl-1,2-diazirine	23.4	70	66.8 [e]	105.0 [d]	1.6	Pass
765-31-1	3-methyl-1,2-diazirine	23.4	30	9.6 [f]	45.0 [d]	4.7	Pass
765-31-1	3-methyl-1,2-diazirine	23.4	70	22.3 [g]	105.0 [d]	4.7	Pass

[a] Daily dose calculated based on 30-day TWA and a 30 kg breathing volume of 8.6 m³/day.
[b] Daily dose calucated based on 30-day TWA and a 30 kg breathing volume adjusted for 8-hours/24-hour exposure per day.
[c] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime for a 30 kg patient at 8.6 m³/day.
[d] Tolerable Exposure based on Cramer Class III compound with no predicted genotoxic/mutagenic alerts of 1.5 ug/kg/day.
[e] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime for a 70 kg patient at 20 m³/day.
[f] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime adjusted daily dose for 8-hours out of 24-hour exposure per day (30 kg patient).
[g] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime adjusted daily dose for 8-hours out of 24-hour exposure per day (70 kg patient).

2,3,4,5-tetrahydropyridazine (CAS Number: 694-06-4)

This compound has no specific pre-clinical toxicological data available in scientific literature nor a known daily permissible daily exposure limit. No specific structural information on this compound in order to create a QSAR analysis was available via PubChem or the Hazardous Substances Data Bank (HSDB), and therefore a structural analog was used (3,4,5,6-tetrahydropyridazine CAS Number: 64030-37-1). Derek Nexus predictive software revealed no specific structural alerts for mutagenicity, sensitization, or other toxicological endpoints of note. An analysis with modified Cramer class rules based on the absence of mutagenic/genotoxic alerts from Derek Nexus with the ToxTree software resulted in a Cramer Class II designation. Permissible daily exposure limits are changed to 9 ug/kg bw/day resulting in 270 and 630 ug/day for a 30 and 70 kg patient respectively. Using the 30-day TWA concentration and calculating the daily dose to a 30 kg patient with the adjusted tolerable exposure results in a MOS > 1.0.

Table 9: Additional Analysis for 2,3,4,5-Tetrahydropyridazine, Nirvana DreamStation Moog.

CAS Number	Substance	30-Day TWA (µg/m³)	Patient Size (kg)	Daily Dose (µg/day)	Daily Tolerable Exposure Dose (µg/day)	MOS	Pass/Fail (Pass = MOS > 1.0)
694-06-4	2,3,4,5-tetrahydropyridazine +	9.5	30	81.5 [a]	270.0 [b]	3.3	Pass
694-06-4	2,3,4,5-tetrahydropyridazine +	9.5	70	189.5 [c]	630.0 [b]	3.3	Pass

[+] 3, 4, 5,6 -tetrahydropyridazine used as structural analog.

[a] Daily dose calculated based on 30-day TWA and a 30 kg breathing volume of 8.6 m³/day.
[b] Tolerable Exposure based on Cramer Class II compound with no predicted genotoxic/mutagenic alerts.
[c] Daily dose calculated based on 30-day TWA and a 70 kg breathing volume of 20.0 m³/day.

A related chemical analog which may be the parent compound of this pyridazine, 1H-imidazole, 1,2-dimethyl (CAS Number: 1739-84-0) was also evaluated with the Derek Nexus QSAR software as well as ToxTree. No specific structural alers fired, including mutagenic/genotoxic alerts. ToxTree classified this

compound as a Cramer Class III compound, which suggests that the parent compounds of some of these identified chemistries may be more toxic than their chemical intermediates and or byproducts.

Hazard Identification

Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- (CAS Number 17540-75-9)

This compound has no specific pre-clinical toxicological data available in scientific literature, nor a known daily permissible daily exposure limit. A QSAR analysis with the Derek Nexus predictive software revealed an open structural alert for chromosome damage (in vitro chromosome aberration test) due to it being an alkylphenol. No sensitization or additional bacterial mutagenicity alerts were noted. Due to its potential classification as a mutagen, the TTC value was set to 1.5 ug per day per ICH M7(R1) guidelines. In all scenarios, MOS values are below 1 for both pediatric and adult patient populations, resulting in this chemical being labelled as a confirmed compound of concern.

Table 10: Additional Analysis for Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- Nirvana DreamStation Moog.

CAS Number	Substance	30-Day TWA (µg/m³)	Patient Size (kg)	Daily Dose (µg/day)	Daily Tolerable Exposure Dose (µg/day)	MOS	Pass/Fail (Pass = MOS > 1.0)
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl	23.8	30	68.2 [a]	17.1 [b]	0.3	Fail
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl	23.8	30	9.7 [d]	1.5 [c]	0.2	Fail
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl	23.8	70	158.6 [e]	40 [f]	0.3	Fail
17540-75-9	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl	23.8	70	22.7 [g]	1.5 [c]	0.1	Fail

[a] Daily dose calucated based on 30-day TWA and a 30 kg breathing volume of 8.6 m^3/day adjusted for 8 hours/24 hour exposure per day.
[b] Toxicity threshold of concern (TTC) 17.1 µg/day represents a de-rating of the 40 µg/day adult specific for COPCs present in multiple sample collection periods per ISO 18562-1.
[c] 1.5 ug/day TTC Based Acceptable Intake from Page 11 of ICH M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals. Accounts for all patient weight classes.
[d] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime for 30 kg patient.
[e] Daily dose calculated based on 30-day TWA and a 70 kg breathing volume of 20 m^3/day adjusted for 8 hours/24 hour exposure per day.
[f] Toxicity threshold of concern (TTC) of 40 µg/day is adult specific for COCs present in multiple sample collection periods per ISO 18562-1.
[g] LADD with a 10-year continuous exposure to the 30-day TWA per year over a 70-year lifetime for 70 kg patient.

In addition to the COPCs and COCs, ozone was detected at initial operation in this device. The results were investigated further across multiple devices and tests.

There are a series of mechanisms and reactions that generate ozone. Ozone is commonly developed via:

- Smog/Pollutants/Reactions
- Ultraviolet Light (Natural and Commercial)
- Electrical Discharge (Natural and Commercial)
- Electrolytic Ozone Production

PSN's test setup involves taking compressed air and passing it through a series of purification steps which includes a halogenated hydrocarbon scrubber, multiple filtration steps, and finally a purification step. The final purification step consists of running zero-air generators through the device to purify air into zero-air source gas for equipment such as chromatography instruments (i.e., GC-MS). PSN worked with Parker to determine that ozone should not make it through the zero-air generator.

The test setups are isolated. The test device inlet is connected to the zero-air source through VOC free inert tubing (Silcotek Silcosteel®). The test chambers contain no heating elements internally or other source of sparks outside of the electrical connection to the device, which is not within the air pathway and is isolated from sample collection for VOCs.

It is unlikely ozone was present or introduced through the testing setup.

Detection sensors and measurement equipment can have cross-sensitivity to other VOCs. PSN implemented a UV detection-based sensor and tested twenty-six additional DreamStation devices under project number 700033. Ozone was not detected above the detection threshold (10 parts per billion) for the chemical sensor or above twelve (12) parts per billion in the UV based detector.

Best laboratory practices (i.e., sterile gloves worn during handling of test devices) and effective isolation of the test equipment in a separate space where only VOC testing occurs limits the background sources of VOCs.

Ozone Source Review

Smog/Pollutants/Reactions
The purification system employs a heated system (450 degrees centigrade) and catalyst module. Latent startup/shutdown issues, as unlikely as they may be, are not possible according to Parker. No pollutants were identified during testing and the system is intended to eliminate confounding VOCs. No indications were present that the source of ozone was from the background. Parker indicated it is unlikely for ozone to make it through the purification step of the zero air generators.

Ultraviolet Light (Natural and Commercial)
PSN does not use UV disinfection techniques which have become more popular during the COVID-19 pandemic and was not using commercial UV generation equipment (i.e., QLabs QUV testing) in the days in and around testing of the devices that registered ozone output. It would require ozone to be present

in the environmental background and to become entrained within the device prior to testing. This is an unlikely source as root sourcing occurred and ozone was not detected in the laboratory.

Electrical Discharge (Natural and Commercial)
The test device is isolated from sources of natural/commercial electrical discharge. It is unlikely the electronics from the device would generate ozone/allow it to enter into the gas pathway of the device.

Electrolytic Ozone Production
No sources of electrolytic ozone production are present in the test setup.

Ozone Root Sourcing Conclusions
There are no proven sources of ozone emission in the PSN test setup for ISO 18562-3 testing for the DreamStation devices that detected ozone.

PSN reviewed the device construction. It unlikely that the source of ozone is within the test device itself. The electric motor is a brushless motor and the electronics cabinet of the device, while not hermitically isolated from the breathing pathway would require a negative pressure (vacuum) to be developed to draw air from the electronics compartment of the CPAP. A vacuum was not drawn during testing; this is not expected to be a source of ozone.

PSN also visited the Philips Respironics manufacturing facility to further investigate whether latent ozone, while improbable at best, could have been captured in the device itself as a function of manufacturing. Two PSN employees walked throughout the manufacturing facility with two sensing devices with 0 to 1000 ppb sensitivity and 0 to 5 ppm sensitivity. Ozone was not detected within the manufacturing facility. Therefore, it is unlikely the source is latent source in which the ozone is being captured within the packaging or device itself. The series of investigatory tests that were completed at PSN were intended to provide additional analysis as to the potential risk to patient safety. Eight additional devices were tested at PSN and none of those eight devices emitted ozone at any time point in this investigation. A total of five devices (out of more than forty DreamStation Nirvana devices), as of May 17th 2021, have had ozone detected above the 0.05 ppm health-based threshold using the chemical indicating sensor. No device has registered above 0.012 ppm using the UV detector.

The following conclusions were developed:

- The initial three devices had emission levels above the health-based threshold at initial operation (T=0-hours) and not at any time point after initial operation. This finding led to additional investigations independently at Philips Respironics and PSN.
- Ozone was not detected in background environment testing in the laboratory.
- A technical review with Parker indicated ozone would not survive the purification step of the zero-air generators.
- Ozone was not detected in background production equipment.
- The device components are unlikely to generate ozone.

8. Risk Conclusion

The Nirvana DreamStation platform consists of two devices differentiated by the type of blower (i.e., Moog vs. SK). A series of devices were tested across both platforms to assess the VOC profile. The polyurethane foam is a common material of construction for the DreamStation Nirvana platform. The scientific and peer reviewed literature states the susceptibility of polyurethane foam, specifically polyester based polyurethane, to hydrolysis[6,7,8,9] under normal environmental and other cleaning processes (i.e., ozone[10]).

The four COCs observed in testing of this specific device were:

- Diazine, dimethyl-, a potential emission related to the Polyurethane foam;
- 2,3,4,5-Tetrahydropyridazine, a potential emission related to the Polyurethane foam;
- 3-methyl-1,2-diazirine, a potential emission related to the Polyurethane foam;
- Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl, an emission related to the Polyurethane foam based on the scientific literature.[11,12]

The series of COCs that have been detected, based on chemistry and targeted testing, can likely be assigned as emissions to the polyurethane foam. More specifically, Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl, is a known antioxidant used in manufacturing of Polyurethane foam and the Diazine, dimethyl- structure is similar/equivalent to emissions detected in Polyurethane foam by PSN. These two COCs have MOS values of less than 1.0 for both patient populations.

Additional studies of the foam in its exemplar (i.e., as-manufactured state) in addition to exposure to field use conditions is recommended in order to better understand the potential risk(s) to patient safety of the out of the box device.

A compendium report is being issued which identifies the conclusions for the device platform. This risk conclusion is focused on the VOC profile evaluated for this specific device.

This risk assessment is current as of the final date on the report. As additional information and studies take place, it is possible that a revision to this report will be necessary to properly reflect the risk to patient safety.

[6] https://doi.org/10.1179/2047058413Y.0000000125
[7] https://doi.org/10.1179/sic.2004.49.s2.022
[8] https://doi.org/10.1016/B978-0-323-51133-9.00006-1
[9] http://wrap.warwick.ac.uk/112512
[10] https://doi.org/10.1155/2014/487343
[11] Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- (DTBSBP) - Canada.ca
[12] ARCHIVED - Environment and Climate Change Canada - Evaluating Existing Substances - Assessment report for Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)-

9. Measurement of Uncertainty

Quantification of VOCs during ISO 18562-3 testing occurs via TO-11A (HPLC) and TO-15 (summa cannisters via GC-MS) or TO-17 (thermal desorption tubes via GC-MS). ISO/IEC 17025:2017 requires the reporting of the measurement of uncertainty if it is relevant to the validity of the test results, a customer requests it, or it affects conformity to a specification limit. The measurement of uncertainty is defined as the expression of the statistical dispersion of the values attributed to a measured quantity. The measurement of uncertainty for HPLC (see **Table 11**) and GC-MS (see **Table 12**) are supported by performance in blind testing (proficient testing) conducted by PSN. Substances that are quantified multi-point standards curves and substances quantified with toluene surrogacy have equivalent measurement of uncertainty.

Substances that are quantified with toluene surrogacy are generally over-estimated (i.e., the concentration reported is higher than the actual concentration when quantified using a multi-point standards curve). When a substance is quantified with toluene surrogacy, the *actual* measured value obtained when quantifying against a multi-point standards curve will most often fall outside of the range of toluene surrogacy with the stacked measurement of uncertainty. Considering the toluene surrogacy is also, in the majority of potential cases, an over-estimation of the quantified amount of a substance, this speaks to the degree of conservatism of the methods for detection and quantification and the corresponding risk assessments conducted within ISO 18562-3 testing.

Table 11: HPLC Measurement of Uncertainty.

Parameter	Validity Range	Uncertainty (k=2)	Remarks
Concentration	0.0 – 50.0 ppm	± 10.5%	Test points correspond to four-point calibration curves with $R^2 \geq 0.995$

Table 12: GC-MS Measurement of Uncertainty.

Parameter	Range	Uncertainty (k=2)	Remarks
Concentration	0.0 – 1,000.0 ppm	± 11.0%	Test points correspond to four-point calibration curves with $R^2 \geq 0.995$

Appendix

Derek Nexus Report

Report Information

Report date	Prediction date	Program version
19 April 2021 07:48:15	19 April 2021 07:44:48	Derek Nexus: 6.1.0, Nexus: 2.3.1

Processing Options

Selected Species	Selected Knowledge Base(s)	Reasoning Level
bacterium, mammal	Derek KB 2020 1.0	At least PLAUSIBLE
Perceive tautomers	**Perceive mixtures**	**Match alerts without rules**
Yes	Yes	No
Show Open likelihood	**Show Negative Predictions**	**Show Rapid Prototypes**
Yes	Yes	Yes
Filter nearest neighbours on misclassified features		
Yes		

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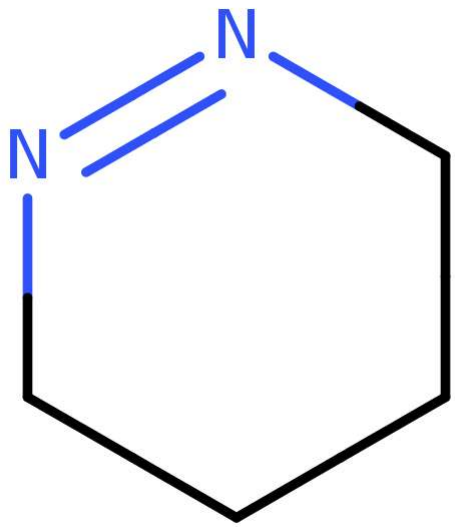
ISO/IEC 17025:2017
Testing Lab Report

Submitted Compound - **64030-37-1**



Smiles: C1CCN=NC1

Exact Mol Mass	84.0687
Average Mol Mass	84.12 (Source: Lhasa Limited, version 1.0)
Log Kp	-2.42 (Source: Potts & Guy, version 1.0)
Log P	1.15 (Source: BioByte Corp., version 5.9)

Predictions

Knowledge Base: Derek KB 2020 1.0

Version	Last Modified Date	Certified by
1.0	26/03/2020 04:28:54	, Leeds, Yorkshire, UK

Reasoning Summary

◆ **Mutagenicity in vitro in bacterium is INACTIVE**
- No misclassified or unclassified features

◆ **Skin sensitisation in mammal is NON-SENSITISER**
- Contains unclassified features

Endpoints not firing any alerts at the selected reasoning level (59)

5alpha-Reductase inhibition	Lachrymation

- Adrenal gland toxicity
- alpha-2-mu-Globulin nephropathy
- Anaphylaxis
- Androgen receptor modulation
- Bladder disorders
- Bladder urothelial hyperplasia
- Blood in urine
- Bone marrow toxicity
- Bradycardia
- Carcinogenicity
- Cardiotoxicity
- Cerebral oedema
- Chloracne
- Cholinesterase inhibition in vitro
- Chromosome damage in vitro genotoxicity in vitro
- Chromosome damage in vivo genotoxicity in vivo
- Cumulative effect on white cell count and immunology
- Cyanide-type effects
- Developmental toxicity
- Glucocorticoid receptor agonism
- Hepatotoxicity
- HERG channel inhibition in vitro
- High acute toxicity
- Irritation (of the eye)
- Irritation (of the gastrointestinal tract)
- Irritation (of the respiratory tract)
- Irritation (of the skin)
- Kidney disorders
- Kidney function-related toxicity
- Methaemoglobinaemia
- Mitochondrial dysfunction
- Mutagenicity in vivo
- Nephrotoxicity
- Neurotoxicity
- Non-specific genotoxicity in vitro
- Non-specific genotoxicity in vivo
- Occupational asthma
- Ocular toxicity
- Oestrogen receptor modulation
- Oestrogenicity
- Peroxisome proliferation
- Phospholipidosis
- Photo-induced chromosome damage in vitro
- Photo-induced non-specific genotoxicity in vitro
- Photo-induced non-specific genotoxicity in vivo
- Photoallergenicity
- Photocarcinogenicity
- Photomutagenicity in vitro
- Phototoxicity
- Pulmonary toxicity
- Respiratory sensitisation
- Splenotoxicity
- Teratogenicity
- Testicular toxicity
- Thyroid toxicity
- Uncoupler of oxidative phosphorylation
- Urolithiasis

Alert Descriptions

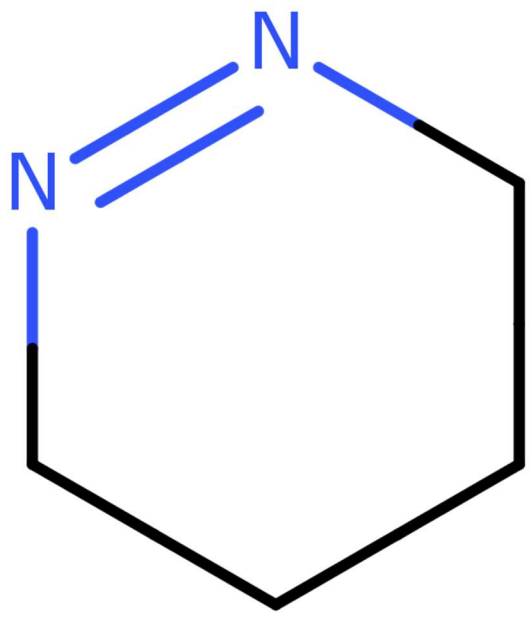
No alerts fired

Reasoning Details

Mutagenicity in vitro in bacterium is INACTIVE (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause mutagenicity; your selected species, which is bacterium.

Overview
No misclassified or unclassified features



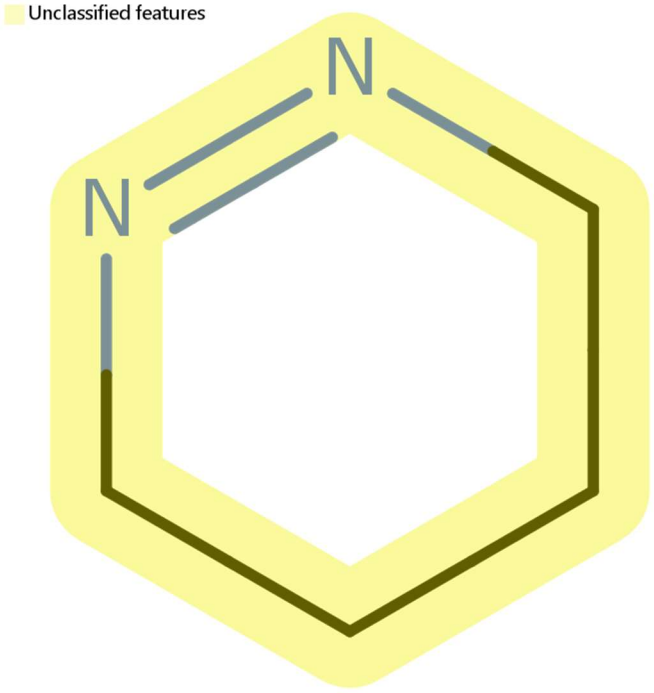
Details
The query structure does not match any structural alerts or examples for (bacterial in vitro) mutagenicity in Derek. Additionally, the query structure does not contain any unclassified or misclassified features and is consequently predicted to be inactive in the bacterial in vitro (Ames) mutagenicity test.

Skin sensitisation in mammal is NON-SENSITISER (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause skin sensitisation; your selected species, which is mammal.

Overview

Contains unclassified features



Details

The query structure contains features (highlighted in the structure panel) that were not found in the Lhasa skin sensitisation negative prediction dataset and do not match any structural alerts or examples for skin sensitisation in Derek. It is predicted to be a non-sensitiser.

Glossary

Certain
There is proof that the proposition is true.

Probable
There is at least one strong argument that the proposition is true and there are no arguments against it.

Plausible
The weight of evidence supports the proposition.

Equivocal
There is an equal weight of evidence for and against the proposition.

Doubted
The weight of evidence opposes the proposition.

Improbable
There is at least one strong argument that the proposition is false and there are no arguments that it is true.

Impossible
There is proof that the proposition is false.

Open
There is no evidence that supports or opposes the proposition.

Contradicted
There is proof that the proposition is both true and false.

Inactive, no misclassified or unclassified features
The query structure does not match any structural alerts or examples in Derek which show activity in a bacterial reverse mutation assay (Ames test). Additionally, the query structure does not contain any unclassified or misclassified features.

Inactive, contains misclassified features
Features in the molecule are found in non-alerting mutagens in the Lhasa reference set. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains unclassified features
Some features in the molecule have not been found in the Lhasa reference set. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains misclassified and unclassified features
The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

Non-sensitiser, no misclassified or unclassified features
The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.

Non-sensitiser, contains misclassified features
Features in the molecule are found in non-alerting sensitisers in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains unclassified features

Some features in the molecule have not been found in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains misclassified and unclassified features

The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

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ISO/IEC 17025:2017
Testing Lab Report

Derek Nexus Report

Report Information

Report date	Prediction date	Program version
19 April 2021 07:47:59	16 April 2021 11:15:51	Derek Nexus: 6.1.0, Nexus: 2.3.1

Processing Options

Selected Species	Selected Knowledge Base(s)	Reasoning Level
bacterium, mammal	Derek KB 2020 1.0	At least PLAUSIBLE
Perceive tautomers	**Perceive mixtures**	**Match alerts without rules**
Yes	Yes	No
Show Open likelihood	**Show Negative Predictions**	**Show Rapid Prototypes**
Yes	Yes	Yes
Filter nearest neighbours on misclassified features		
Yes		

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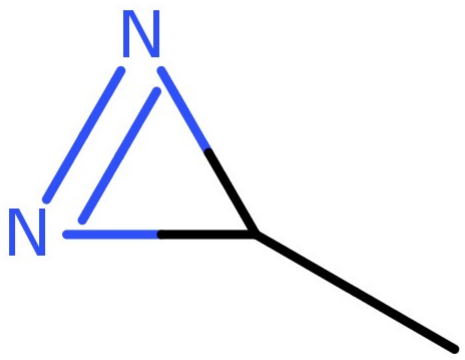
ISO/IEC 17025:2017
Testing Lab Report

Submitted Compound - **765-31-1**



Smiles: CC1N=N1

Exact Mol Mass	56.0374
Average Mol Mass	56.07 (Source: Lhasa Limited, version 1.0)
Log Kp	-2.7 (Source: Potts & Guy, version 1.0)
Log P	0.51 (Source: BioByte Corp., version 5.9)

Predictions

Knowledge Base: Derek KB 2020 1.0

Version	Last Modified Date	Certified by
1.0	26/03/2020 04:28:54	, Leeds, Yorkshire, UK

Reasoning Summary

◆ **Mutagenicity in vitro in bacterium is INACTIVE**
- Contains unclassified features

◆ **Skin sensitisation in mammal is NON-SENSITISER**
- Contains unclassified features

Endpoints not firing any alerts at the selected reasoning level (59)

5alpha-Reductase inhibition	Lachrymation

- Adrenal gland toxicity
- alpha-2-mu-Globulin nephropathy
- Anaphylaxis
- Androgen receptor modulation
- Bladder disorders
- Bladder urothelial hyperplasia
- Blood in urine
- Bone marrow toxicity
- Bradycardia
- Carcinogenicity
- Cardiotoxicity
- Cerebral oedema
- Chloracne
- Cholinesterase inhibition in vitro
- Chromosome damage in vitro genotoxicity in vitro
- Chromosome damage in vivo genotoxicity in vivo
- Cumulative effect on white cell count and immunology
- Cyanide-type effects
- Developmental toxicity
- Glucocorticoid receptor agonism
- Hepatotoxicity
- HERG channel inhibition in vitro
- High acute toxicity
- Irritation (of the eye)
- Irritation (of the gastrointestinal tract)
- Irritation (of the respiratory tract)
- Irritation (of the skin)
- Kidney disorders
- Kidney function-related toxicity
- Methaemoglobinaemia
- Mitochondrial dysfunction
- Mutagenicity in vivo
- Nephrotoxicity
- Neurotoxicity
- Non-specific genotoxicity in vitro
- Non-specific genotoxicity in vivo
- Occupational asthma
- Ocular toxicity
- Oestrogen receptor modulation
- Oestrogenicity
- Peroxisome proliferation
- Phospholipidosis
- Photo-induced chromosome damage in vitro
- Photo-induced non-specific genotoxicity in vitro
- Photo-induced non-specific genotoxicity in vivo
- Photoallergenicity
- Photocarcinogenicity
- Photomutagenicity in vitro
- Phototoxicity
- Pulmonary toxicity
- Respiratory sensitisation
- Splenotoxicity
- Teratogenicity
- Testicular toxicity
- Thyroid toxicity
- Uncoupler of oxidative phosphorylation
- Urolithiasis

Alert Descriptions

No alerts fired

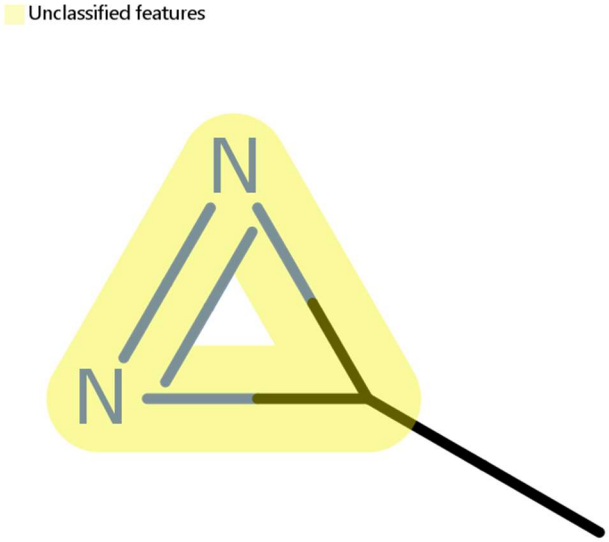
Reasoning Details

Mutagenicity in vitro in bacterium is INACTIVE (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause mutagenicity; your selected species, which is bacterium.

Overview

Contains unclassified features



Details

The query structure contains features (highlighted in the structure panel) that were not found in the Lhasa Ames test reference set and do not match any structural alerts or examples for (bacterial in vitro) mutagenicity in Derek. It is predicted to be inactive in the bacterial in vitro (Ames) mutagenicity test.

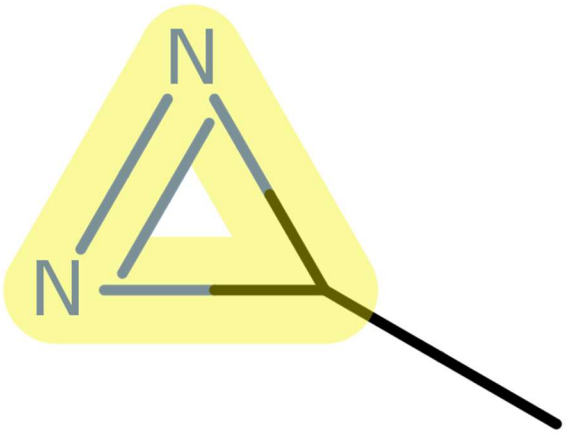
Skin sensitisation in mammal is NON-SENSITISER (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause skin sensitisation; your selected species, which is mammal.

Overview

Contains unclassified features

Unclassified features



Details

The query structure contains features (highlighted in the structure panel) that were not found in the Lhasa skin sensitisation negative prediction dataset and do not match any structural alerts or examples for skin sensitisation in Derek. It is predicted to be a non-sensitiser.

Glossary

Certain
There is proof that the proposition is true.

Probable
There is at least one strong argument that the proposition is true and there are no arguments against it.

Plausible
The weight of evidence supports the proposition.

Equivocal
There is an equal weight of evidence for and against the proposition.

Doubted
The weight of evidence opposes the proposition.

Improbable
There is at least one strong argument that the proposition is false and there are no arguments that it is true.

Impossible
There is proof that the proposition is false.

Open
There is no evidence that supports or opposes the proposition.

Contradicted
There is proof that the proposition is both true and false.

Inactive, no misclassified or unclassified features
The query structure does not match any structural alerts or examples in Derek which show activity in a bacterial reverse mutation assay (Ames test). Additionally, the query structure does not contain any unclassified or misclassified features.

Inactive, contains misclassified features
Features in the molecule are found in non-alerting mutagens in the Lhasa reference set. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains unclassified features
Some features in the molecule have not been found in the Lhasa reference set. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains misclassified and unclassified features
The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

Non-sensitiser, no misclassified or unclassified features
The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.

Non-sensitiser, contains misclassified features
Features in the molecule are found in non-alerting sensitisers in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains unclassified features

Some features in the molecule have not been found in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains misclassified and unclassified features

The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

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Derek Nexus Report

Report Information

Report date	Prediction date	Program version
19 April 2021 07:47:38	16 April 2021 08:44:21	Derek Nexus: 6.1.0, Nexus: 2.3.1

Processing Options

Selected Species	Selected Knowledge Base(s)	Reasoning Level
bacterium, mammal	Derek KB 2020 1.0	At least PLAUSIBLE
Perceive tautomers	**Perceive mixtures**	**Match alerts without rules**
Yes	Yes	No
Show Open likelihood	**Show Negative Predictions**	**Show Rapid Prototypes**
Yes	Yes	Yes
Filter nearest neighbours on misclassified features		
Yes		

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ISO/IEC 17025:2017
Testing Lab Report

Submitted Compound - **503-28-6**

Smiles: CN=NC

Exact Mol Mass	58.0531
Average Mol Mass	58.08 (Source: Lhasa Limited, version 1.0)
Log Kp	-2.63 (Source: Potts & Guy, version 1.0)
Log P	0.63 (Source: BioByte Corp., version 5.9)

Predictions

Knowledge Base: Derek KB 2020 1.0

Version	Last Modified Date	Certified by
1.0	26/03/2020 04:28:54	Leeds, Yorkshire, UK

Reasoning Summary

◆ **Mutagenicity in vitro in bacterium is INACTIVE**
- No misclassified or unclassified features

◆ **Skin sensitisation in mammal is NON-SENSITISER**
- No misclassified or unclassified features

Endpoints not firing any alerts at the selected reasoning level (59)

5alpha-Reductase inhibition	Lachrymation

- Adrenal gland toxicity
- alpha-2-mu-Globulin nephropathy
- Anaphylaxis
- Androgen receptor modulation
- Bladder disorders
- Bladder urothelial hyperplasia
- Blood in urine
- Bone marrow toxicity
- Bradycardia
- Carcinogenicity
- Cardiotoxicity
- Cerebral oedema
- Chloracne
- Cholinesterase inhibition in vitro
- Chromosome damage in vitro genotoxicity in vitro
- Chromosome damage in vivo genotoxicity in vivo
- Cumulative effect on white cell count and immunology
- Cyanide-type effects
- Developmental toxicity
- Glucocorticoid receptor agonism
- Hepatotoxicity
- HERG channel inhibition in vitro
- High acute toxicity
- Irritation (of the eye)
- Irritation (of the gastrointestinal tract)
- Irritation (of the respiratory tract)
- Irritation (of the skin)
- Kidney disorders
- Kidney function-related toxicity
- Methaemoglobinaemia
- Mitochondrial dysfunction
- Mutagenicity in vivo
- Nephrotoxicity
- Neurotoxicity
- Non-specific genotoxicity in vitro
- Non-specific genotoxicity in vivo
- Occupational asthma
- Ocular toxicity
- Oestrogen receptor modulation
- Oestrogenicity
- Peroxisome proliferation
- Phospholipidosis
- Photo-induced chromosome damage in vitro
- Photo-induced non-specific genotoxicity in vitro
- Photo-induced non-specific genotoxicity in vivo
- Photoallergenicity
- Photocarcinogenicity
- Photomutagenicity in vitro
- Phototoxicity
- Pulmonary toxicity
- Respiratory sensitisation
- Splenotoxicity
- Teratogenicity
- Testicular toxicity
- Thyroid toxicity
- Uncoupler of oxidative phosphorylation
- Urolithiasis

Alert Descriptions

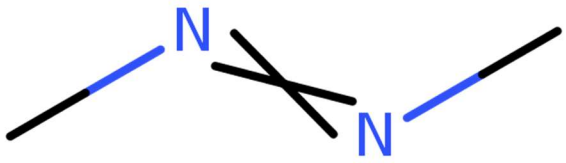
No alerts fired

Reasoning Details

Mutagenicity in vitro in bacterium is INACTIVE (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause mutagenicity; your selected species, which is bacterium.

Overview
No misclassified or unclassified features



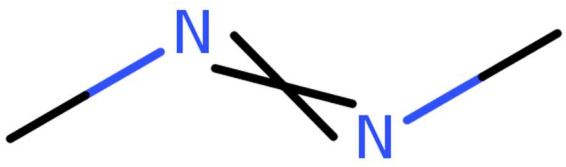
Details
The query structure does not match any structural alerts or examples for (bacterial in vitro) mutagenicity in Derek. Additionally, the query structure does not contain any unclassified or misclassified features and is consequently predicted to be inactive in the bacterial in vitro (Ames) mutagenicity test.

Skin sensitisation in mammal is NON-SENSITISER (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause skin sensitisation; your selected species, which is mammal.

Overview

No misclassified or unclassified features



Details

The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features and is consequently predicted to be a non-sensitiser.

Glossary

Certain
There is proof that the proposition is true.

Probable
There is at least one strong argument that the proposition is true and there are no arguments against it.

Plausible
The weight of evidence supports the proposition.

Equivocal
There is an equal weight of evidence for and against the proposition.

Doubted
The weight of evidence opposes the proposition.

Improbable
There is at least one strong argument that the proposition is false and there are no arguments that it is true.

Impossible
There is proof that the proposition is false.

Open
There is no evidence that supports or opposes the proposition.

Contradicted
There is proof that the proposition is both true and false.

Inactive, no misclassified or unclassified features
The query structure does not match any structural alerts or examples in Derek which show activity in a bacterial reverse mutation assay (Ames test). Additionally, the query structure does not contain any unclassified or misclassified features.

Inactive, contains misclassified features
Features in the molecule are found in non-alerting mutagens in the Lhasa reference set. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains unclassified features
Some features in the molecule have not been found in the Lhasa reference set. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains misclassified and unclassified features
The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

Non-sensitiser, no misclassified or unclassified features
The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.

Non-sensitiser, contains misclassified features
Features in the molecule are found in non-alerting sensitisers in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains unclassified features

Some features in the molecule have not been found in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains misclassified and unclassified features

The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

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Lhasa Limited

Derek nexus

Derek Nexus Report

Report Information

Report date	Prediction date	Program version
12 May 2021 15:16:53	12 May 2021 14:35:55	Derek Nexus: 6.1.0, Nexus: 2.3.1

Processing Options

Selected Species	Selected Knowledge Base(s)	Reasoning Level
bacterium, mammal	Derek KB 2020 1.0	At least PLAUSIBLE
Perceive tautomers	**Perceive mixtures**	**Match alerts without rules**
Yes	Yes	No
Show Open likelihood	**Show Negative Predictions**	**Show Rapid Prototypes**
Yes	Yes	Yes
Filter nearest neighbours on misclassified features		
Yes		

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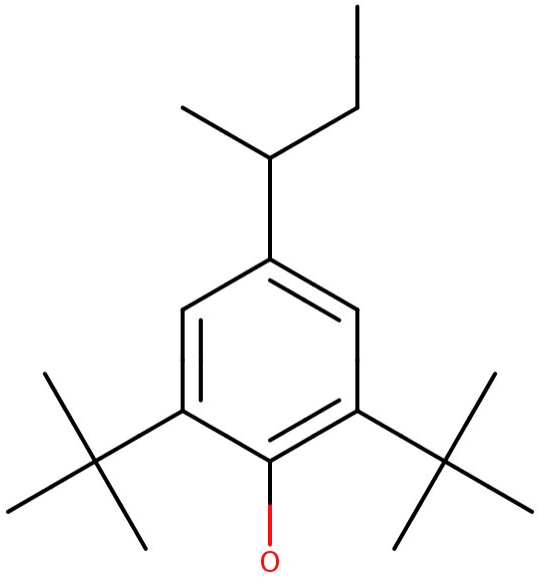
ISO/IEC 17025:2017
Testing Lab Report

Submitted Compound - **17540-75-9**



Smiles: CCC(C)C1=CC(=C(C(=C1)C(C)(C)C)O)C(C)(C)C

Exact Mol Mass	262.2297
Average Mol Mass	262.43 (Source: Lhasa Limited, version 1.0)
Log Kp	0.35 (Source: Potts & Guy, version 1.0)
Log P	6.58 (Source: BioByte Corp., version 5.9)

Predictions

Knowledge Base: Derek KB 2020 1.0

Version	Last Modified Date	Certified by
1.0	26/03/2020 02:28:54	, Leeds, Yorkshire, UK

Reasoning Summary

◆ **Chromosome damage in vitro in mammal is OPEN**
- Alert matched: 523 Alkylphenol

◆ **Mutagenicity in vitro in bacterium is INACTIVE**
- No misclassified or unclassified features

◆ **Skin sensitisation in mammal is NON-SENSITISER**
- No misclassified or unclassified features

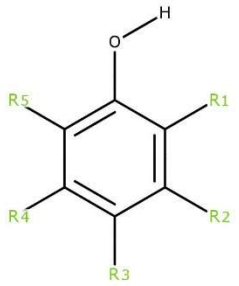
Endpoints not firing any alerts at the selected reasoning level (58)

5alpha-Reductase inhibition	Lachrymation
Adrenal gland toxicity	Methaemoglobinaemia
alpha-2-mu-Globulin nephropathy	Mitochondrial dysfunction
Anaphylaxis	Mutagenicity in vivo
Androgen receptor modulation	Nephrotoxicity
Bladder disorders	Neurotoxicity
Bladder urothelial hyperplasia	Non-specific genotoxicity in vitro
Blood in urine	Non-specific genotoxicity in vivo
Bone marrow toxicity	Occupational asthma
Bradycardia	Ocular toxicity
Carcinogenicity	Oestrogen receptor modulation
Cardiotoxicity	Oestrogenicity
Cerebral oedema	Peroxisome proliferation
Chloracne	Phospholipidosis
Cholinesterase inhibition	Photo-induced chromosome damage in vitro
Chromosome damage in vivo	Photo-induced non-specific genotoxicity in vitro
Cumulative effect on white cell count and immunology	Photo-induced non-specific genotoxicity in vivo
Cyanide-type effects	Photoallergenicity
Developmental toxicity	Photocarcinogenicity
Glucocorticoid receptor agonism	Photomutagenicity in vitro
Hepatotoxicity	Phototoxicity
HERG channel inhibition in vitro	Pulmonary toxicity
High acute toxicity	Respiratory sensitisation
Irritation (of the eye)	Splenotoxicity
Irritation (of the gastrointestinal tract)	Teratogenicity
Irritation (of the respiratory tract)	Testicular toxicity
Irritation (of the skin)	Thyroid toxicity
Kidney disorders	Uncoupler of oxidative phosphorylation
Kidney function-related toxicity	Urolithiasis

Alert Descriptions

Alert: 523 Alkylphenol (from KB: Derek KB 2020 1.0)

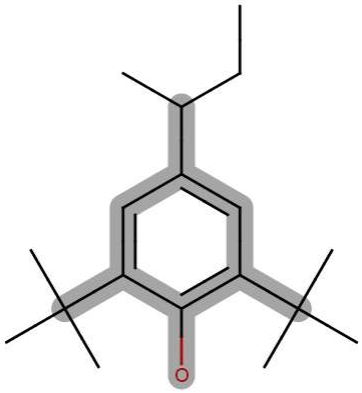
Alert Description Image



R1-R5 = H, C (alkyl)
At least one of R1-R5 must be C (alkyl)

Oestrogens are excluded

Match with query compound



Comments

Chromosome damage (clastogenicity): in vitro chromosome aberration test

This alert describes the activity of alkylphenols in the in vitro chromosome aberration test and is based upon a dataset of forty-four compounds donated by a Lhasa Limited member.

Activity in the chromosome aberration test is generally observed for alkylphenols with a log P value of three or less. This is an arbitrary value chosen after analysis of the donated dataset where activity was shown to be less likely for those compounds with a higher log P. This observation is supported by data in the published literature where m-cresol [Hikiba et al], 4-(1-methylpropyl)phenol and p-tert-butylphenol [Kusakabe et al] and thymol [Kusakabe et al, Hikiba et al] have all been reported active in the in vitro chromosome aberration test. Activity for these compounds is generally promoted by the presence of S9 mix. In contrast, 6-tert-butyl-2,4-xylenol and 4-tert-octylphenol have both been reported inactive [Kusakabe et al].

There are a number of mechanisms by which alkylphenols may induce chromosome damage. The promoting effect of S9 mix suggests that activity may be related to oxidation and the formation of reactive metabolites, including quinols or quinone methides [Ohe et al, Thompson et al]. Phenolic compounds may also have the potential to be uncouplers of oxidative phosphorylation [Terada] and have been shown to generate reactive oxygen species via the interaction of phenoxyl radicals with cellular thiols [Stoyanovsky et al].

References

- Kusakabe H, Yamakage K, Wakuri S, Sasaki K, Nakagawa Y, Watanabe M, Hayashi M, Sofuni T, Ono H and Tanaka N. (2002)
  Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals., *Mutation Research*, 517 , 187-198
  DOI: 10.1016/S1383-5718(02)00062-1
- Hikiba H, Watanabe E, Barrett JC and Tsutsui T. (2005)
  Ability of fourteen chemical agents used in dental practice to induce chromosome aberrations in Syrian hamster embryo cells., *Journal of Pharmacological Sciences*, 97 , 146-152
  DOI: 10.1254/jphs.FPJ04044X
- Terada H. (1990)
  Uncouplers of oxidative phosphorylation., *Environmental Health Perspectives*, 87 , 213-218
- Ohe T, Hirobe M and Mashino T. (2000)
  Novel metabolic pathway of estrone and 17beta-estradiol catalyzed by cytochrome P-450., *Drug Metabolism and Disposition*, 28 , 110-112
- Thompson DC, Perera K and London R (1995)
  Quinone methide formation from para isomers of methylphenol (cresol), ethylphenol, and isopropylphenol: relationship to toxicity., *Chemical Research in Toxicology*, 8 , 55-60
- Stoyanovsky DA, Goldman R, Claycamp HG and Kagan VE. (1995)
  Phenoxyl radical-induced thiol-dependent generation of reactive oxygen species: implications for benzene toxicity., *Archives of Biochemistry and Biophysics*, 317 , 315-323

Validation comments

Chromosome damage: in vitro chromosome aberration test

The alert has demonstrated the following predictive performance:

1) Sofuni data set: 1 compound activates this alert of which 0 are reported positive (positive predictivity = 0%)
2) FDA CFSAN data set: 22 compounds activate this alert of which 12 are reported positive (positive predictivity = 55%)
3) CGX data set: 2 compounds activate this alert of which 1 is reported positive (positive predictivity = 50%)

1) A collection of in vitro chromosome aberration test data for 712 compounds from the following source: Revised Edition 1998 Data Book of Chromosomal Aberration Test in Vitro, Sofuni T (editor), Life-Science Information Center, Tokyo, 1999.

2) A collection of in vitro chromosome aberration test data for 2172 compounds derived from the FDA/CFSAN/OFAS knowledge base.

3) A collection of in vitro chromosome aberration test data for 488 compounds from the following reference: Kirkland D, Aardema M, Henderson L and Muller L. Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens. I. Sensitivity, specificity and relative predictivity. Mutation Research, 2005, 584, 1-256, available at "http://dx.doi.org/10.1016/j.mrgentox.2005.02.004".

In assessing predictive performance, it should be noted that:

- Mammalian in vitro chromosome damage predictions in Derek associated with a reasoning level of equivocal or above have been considered positive;

- Predictions do not take into account (i) the tautomeric forms of compounds or (ii) the individual components of mixtures;

- The classification of compounds from the Sofuni data set as positive or negative is based upon an overall result which includes both polyploidy and structural chromosome aberration results;

- The classification of compounds from the FDA CFSAN data set as positive or negative is based upon a composite activity score for aberrations in vitro;

- Compounds in the data sets assigned responses other than positive or negative have been excluded from the analysis;

- No account has been taken of other chromosome damage alerts which may also be present in some compounds;

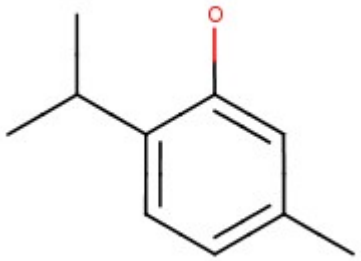
- No comparison has been made between the protocol used to obtain positive experimental results, including exposure time and metabolic activation, and the expected profile which may be included in the comments for an alert;

- Information from the data sets may have been used previously as supporting evidence for the derivation of some alerts;

- Some compounds may be present in more than one of the data sets analysed.

Examples for Alert 523 Alkylphenol

Example 1: thymol



CAS Registry Number®: 89-83-8

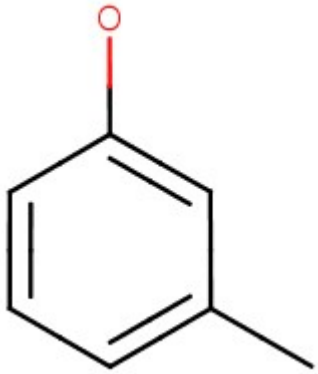
Test Data (thymol)

1)	Species	Assay	Endpoint(s)	Result
	hamster	in vitro chromosome aberration test	Chromosome damage in vitro	positive

References

- Hikiba H, Watanabe E, Barrett JC and Tsutsui T. (2005)
  Ability of fourteen chemical agents used in dental practice to induce chromosome aberrations in Syrian hamster embryo cells., *Journal of Pharmacological Sciences*, 97 , 146-152
  DOI: 10.1254/jphs.FPJ04044X
- Kusakabe H, Yamakage K, Wakuri S, Sasaki K, Nakagawa Y, Watanabe M, Hayashi M, Sofuni T, Ono H and Tanaka N. (2002)
  Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals., *Mutation Research*, 517 , 187-198
  DOI: 10.1016/S1383-5718(02)00062-1

Example 2: m-cresol



CAS Registry Number®: 108-39-4

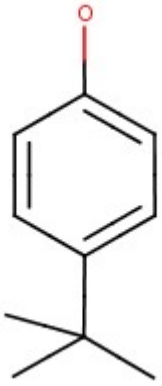
Test Data (m-cresol)

	Species	Assay	Endpoint(s)	Result
1)	hamster	in vitro chromosome aberration test	Chromosome damage in vitro	positive

References

- Hikiba H, Watanabe E, Barrett JC and Tsutsui T. (2005)
  Ability of fourteen chemical agents used in dental practice to induce chromosome aberrations in Syrian hamster embryo cells., *Journal of Pharmacological Sciences*, 97 , 146-152
  DOI: 10.1254/jphs.FPJ04044X

Example 3: 4-tert-butylphenol



CAS Registry Number®: 98-54-4

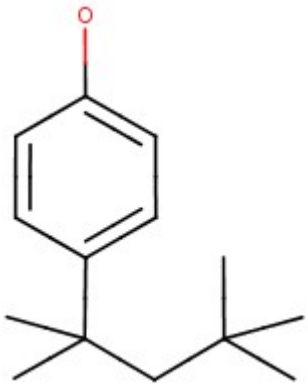
Test Data (4-tert-butylphenol)

	Species	Assay	Endpoint(s)	Result
1)	hamster	in vitro chromosome aberration test	Chromosome damage in vitro	positive

References

- Kusakabe H, Yamakage K, Wakuri S, Sasaki K, Nakagawa Y, Watanabe M, Hayashi M, Sofuni T, Ono H and Tanaka N. (2002)
  Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals., *Mutation Research*, 517 , 187-198
  DOI: 10.1016/S1383-5718(02)00062-1

Example 4: 4-tert-octylphenol



CAS Registry Number®: 140-66-9

Test Data (4-tert-octylphenol)

	Species	Assay	Endpoint(s)	Result
1)	hamster	in vitro chromosome aberration test	Chromosome damage in vitro	negative

References

- Kusakabe H, Yamakage K, Wakuri S, Sasaki K, Nakagawa Y, Watanabe M, Hayashi M, Sofuni T, Ono H and Tanaka N. (2002)
  Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals., *Mutation Research*, 517 , 187-198
  DOI: 10.1016/S1383-5718(02)00062-1

Reasoning Details

Chromosome damage in vitro in mammal is OPEN (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause chromosome damage; your selected species, which is mammal.

Rule 768: If [species mammal] is [certain] then [Species dependent variable 35] is [Log P dependent variable 2]

- species mammal **is** CERTAIN

If the chemical has a Log P value of less than 3 then in mammals the variable "Species dependent variable 35" is plausible. The variation in rule outcome with Log P is achieved via use of the variable "Log P dependent variable 2".

Rule 766: If [alert 523] is [certain] then [Chromosome damage in vitro] is [Species dependent variable 35]

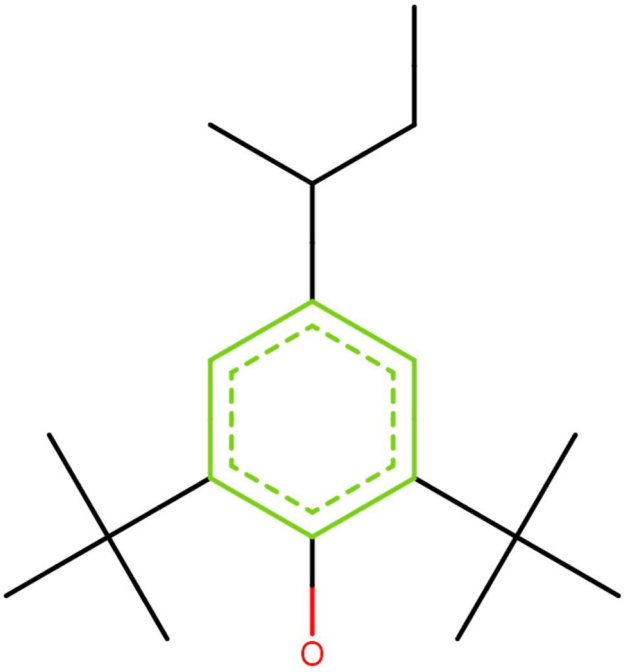
- alert 523 **is** CERTAIN
- Species dependent variable 35 **is** OPEN

If a chemical contains alert 523 then it is considered plausible that the chemical will cause chromosome damage in vitro in mammals if the chemical also has a Log P value of less than 3 and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 35".

Mutagenicity in vitro in bacterium is INACTIVE (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause mutagenicity; your selected species, which is bacterium.

Overview
No misclassified or unclassified features

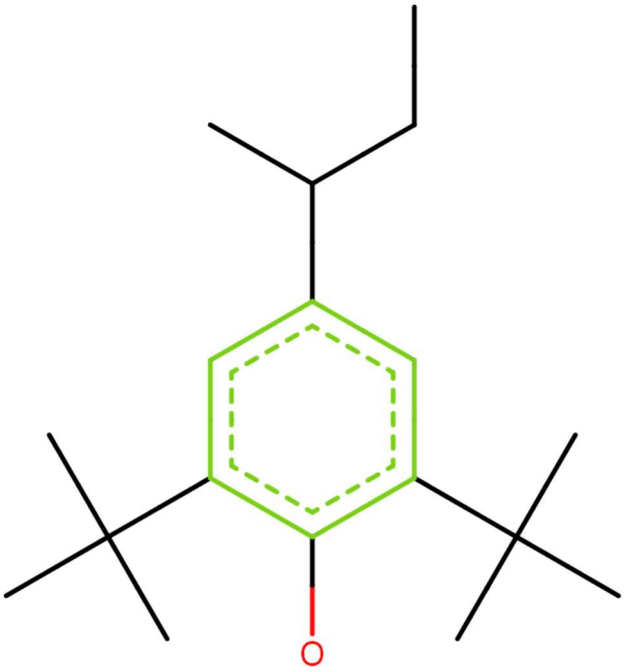


Details
The query structure does not match any structural alerts or examples for (bacterial in vitro) mutagenicity in Derek. Additionally, the query structure does not contain any unclassified or misclassified features and is consequently predicted to be inactive in the bacterial in vitro (Ames) mutagenicity test.

Skin sensitisation in mammal is NON-SENSITISER (from KB: Derek KB 2020 1.0)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause skin sensitisation; your selected species, which is mammal.

Overview
No misclassified or unclassified features



Details

The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features and is consequently predicted to be a non-sensitiser.

Glossary

Certain
There is proof that the proposition is true.

Probable
There is at least one strong argument that the proposition is true and there are no arguments against it.

Plausible
The weight of evidence supports the proposition.

Equivocal
There is an equal weight of evidence for and against the proposition.

Doubted
The weight of evidence opposes the proposition.

Improbable
There is at least one strong argument that the proposition is false and there are no arguments that it is true.

Impossible
There is proof that the proposition is false.

Open
There is no evidence that supports or opposes the proposition.

Contradicted
There is proof that the proposition is both true and false.

Inactive, no misclassified or unclassified features
The query structure does not match any structural alerts or examples in Derek which show activity in a bacterial reverse mutation assay (Ames test). Additionally, the query structure does not contain any unclassified or misclassified features.

Inactive, contains misclassified features
Features in the molecule are found in non-alerting mutagens in the Lhasa reference set. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains unclassified features
Some features in the molecule have not been found in the Lhasa reference set. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains misclassified and unclassified features
The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

Non-sensitiser, no misclassified or unclassified features
The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.

Non-sensitiser, contains misclassified features
Features in the molecule are found in non-alerting sensitisers in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains unclassified features

Some features in the molecule have not been found in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains misclassified and unclassified features

The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

CAS Registry Numbers® (CAS RN®)

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The data interpretation may fall outside the boundaries of the reporting required by the ISO/EPA standards and relies upon the subject matter experts (SME's) and their experience, historical understanding of the test method and/or types of test/sample, and its relation to the work completed in this test program. These expert opinions are intended to provide context to the results. These opinions often draw on client supplied information regarding the samples, their life exposure environment, and their manufacturing method. PSN does not independently verify these statements for accuracy and thus assumes they are accurate for interpretation purposes. Our team of SME's provides thoughtful and insightful interpretation with the intended goal of providing value to the data.

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