DIACETONE ALCOHOL

(CAS #123-42-2)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

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GreenScreen® Executive Summary for Diacetone Alcohol (CAS #123-42-2)

Diacetone alcohol is used as a chemical intermediate in the synthesis of mesityl oxide, hexylene glycol, and other organic chemicals; as a solvent for cellulose acetate, nitrocellulose, celluloid fats, oils, waxes, resins, and paint; and as a preservative in pharmaceutical preparations. Diacetone alcohol is a colorless liquid at room temperature. It is highly soluble in water. Its measured vapor pressure of 0.97 mm Hg indicates that it will likely volatilize.

Diacetone alcohol was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combination:

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C, developmental toxicity-D, and endocrine activity-E)

The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with version 1.4 updates in 2019, and with this most recent update in 2023.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for respiratory sensitization, persistence, and bioaccumulation, and *in vitro* testing for genotoxicity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

Type I (input data) uncertainties in diacetone alcohol's NAMs dataset include lack of experimental data and validated test methods for respiratory sensitization. Diacetone alcohol's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of diacetone alcohol's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Diacetone Alcohol

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	**L**	**M**	*M*	**L**	*H*	**L**	**M**	**L**	**L**	*L*	*L*	**H**	**L**	*L*	**vL**	**vL**	*L*	**M**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for Diacetone Alcohol (CAS #123-42-2)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.2) Prepared By:
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Date: September 18, 2014

Quality Control Performed By:
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Date: September 19, 2014

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Date: April 10, 2019

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Date: January 4, 2023

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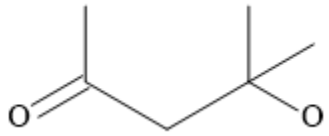
Organization: ToxServices LLC
Date: January 25, 2023

Expiration Date: January 25, 2028[2]

Chemical Name: Diacetone alcohol

CAS Number: 123-42-2

Chemical Structure(s):

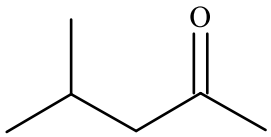


Also called:
4-Hydroxy-4-methyl-2-pentanone (PubChem 2023).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Diacetone alcohol has a relatively complete toxicological dataset. ToxServices identified methyl isobutyl ketone (MIBK, CAS #108-10-1) as a surrogate for the inhalation route of exposure. Available *in vivo* toxicokinetic studies in rats showed that diacetone alcohol is an expected metabolite after

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

inhalation exposure to methyl isobutyl ketone (ECHA 2018a). However, it is not detected after oral route exposure (ECHA 2018a). Further, the European Chemicals Agency (ECHA) evaluated the REACH registration dossier for diacetone alcohol and concluded that methyl isobutyl ketone has different metabolism after oral and inhalation administration and its metabolism to diacetone alcohol is expected to be slow (ECHA 2014). Based on these factors, ToxServices considered methyl isobutyl ketone as a weak surrogate and only its inhalation toxicity data were considered.



Methyl isobutyl ketone ((CAS #108-10-1)

Identify Applications/Functional Uses (Pharos 2023)**:**
1. Chemical intermediate
2. Solvent
3. Preservative

Known Impurities[3]:
Diacetone alcohol may contain acetone as an impurity (ECHA 2023a).

GreenScreen® Summary Rating for Diacetone Alcohol[4,5 6,7]: Diacetone Alcohol was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C, developmental toxicity-D, and endocrine activity-E)

Figure 1: GreenScreen® Hazard Summary Table for Diacetone Alcohol

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	**L**	**M**	*M*	**L**	*H*	**L**	**M**	**L**	**L**	*L*	*L*	**H**	**L**	*L*	**vL**	**vL**	*L*	**M**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As diacetone alcohol is readily biodegradable, it is not expected to have relevant transformation products.

Introduction

Diacetone alcohol is used as a chemical intermediate in the synthesis of mesityl oxide, hexylene glycol, and other organic chemicals; as a solvent for cellulose acetate, nitrocellulose, celluloid fats, oils, waxes, resins, and paint; and as a preservative in pharmaceutical preparations (UNEP 2000). Diacetone alcohol is manufactured by the reaction of barium hydroxide, calcium hydroxide or potassium hydroxide with acetone (PubChem 2023).

ToxServices assessed diacetone alcohol against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2023). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Diacetone alcohol is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for diacetone alcohol can be found in Appendix C.

- Diacetone alcohol is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Diacetone alcohol is listed on the following GreenScreen®-specified lists for multiple endpoints
  - German FEA – Substances hazardous to waters: Class 1 – How hazard to waters.
  - Québec CSST – WHMIS 1988: Class D2B – Toxic material causing other toxic effects.
  - EC – CEPA DSL: Inherently toxic to humans (iTH)
- Lists for single endpoints are included below in the evaluation of individual endpoints.
- Diacetone alcohol is not listed on the U.S. DOT list.

[8] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

Hazard Statement and Occupational Control

Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for diacetone alcohol, as indicated in Table 1. General personal protective equipment (PPE) recommendations and occupational exposure limits (OELs) are presented in Table 2, below.

Table 1: GHS H Statements for Diacetone Alcohol (CAS #123-42-2) (ECHA 2023a)

H Statement	H Statement Details
H319	Causes serious eye irritation

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Diacetone Alcohol (CAS #123-42-2)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Wear chemical resistant gloves and chemical splash goggles and use breathing apparatus only where risk assessment shows air-purifying respirators are appropriate.	Sigma-Aldrich 2021	PEL (TWA): 50 ppm (240 mg/m^3) TLV (TWA): 50 ppm IDLH: 1800 ppm	OSHA 2020

TLV (ACGIH Threshold Limit Values)
PEL: Permissible Exposure Limit
TWA: Time Weighted Average
ACGIH - American Conference of Governmental Industrial Hygienists
OSHA - Occupational Safety and Health Administration
NIOSH IDLH: The National Institute for Occupational Safety and Health Immediately Dangerous to Life or Health

Physicochemical Properties of Diacetone Alcohol

Diacetone alcohol is a colorless liquid at room temperature. It is highly soluble in water. Its measured vapor pressure of 0.97 mm Hg indicates that it is likely to volatilize. Its measured low log K_{ow} indicates that it is not likely to bioaccumulate.

Table 3: Physical and Chemical Properties of Diacetone Alcohol (CAS #123-42-2)

Property	Value	Reference
Molecular formula	$C_6H_{12}O_2$	PubChem 2023
SMILES Notation	CC(=O)CC(C)(C)O	PubChem 2023
Molecular weight	116.16 g/mol	PubChem 2023
Physical state	Liquid	ECHA 2023a
Appearance	Colorless liquid with faint odor	ECHA 2023a
Melting point	-44°C	ECHA 2023a
Boiling point	167.9°C	ECHA 2023a
Vapor pressure	0.97 mm Hg @ 20°C (exp.)	ECHA 2023a
Water solubility	$1x10^6$ mg/L (exp.)	U.S. EPA 2017
Dissociation constant	N/A	
Density/specific gravity	0.94 g/cm^3 @ 20°C	ECHA 2023a
Partition coefficient	Log K_{ow} = -0.14 (exp.)	U.S. EPA 2017

Toxicokinetics

- ECHA 2023a
    - *Absorption:* The low molecular weight, log K_{ow}, and physical state of diacetone alcohol favor its absorption via various routes of exposure (oral, dermal, and inhalation). According

to available data from a pharmacokinetic study in rats, the absorption by the oral and inhalation routes is considered to be extensive and close to 100%, while dermal penetration is assumed to not exceed 1 and 5% for 8- and 24-hour exposures, respectively.
    - *Distribution:* The high water solubility suggests that it readily diffuses through aqueous channels and pores of various tissues and organs; therefore, diacetone alcohol is expected to be evenly distributed throughout the body. In a nose-only 6-hour inhalation study in rats, animals exposed to diacetone alcohol at 2.41 and 5.16 (analytical) mg/L. Diacetone alcohol was detected in the plasma from 0.5 to 24 hours after exposure. Similarly, diacetone alcohol was detected in the plasma from 0.5 to 24 hours after a single oral exposure of 580 mg/kg in Sprague-Dawley rats.
    - *Metabolism:* In a nose-only 6-hour inhalation study in rats, animals exposed to diacetone alcohol at 2.41 and 5.16 (analytical) mg/L. Diacetone alcohol was detected in the plasma from 0.5 to 24 hours after exposure, but no methyl isobutyl ketone or methyl-isobutyl carbinol (MIBC) could be detected in the plasma. No additional information on metabolism was identified.
    - *Elimination:* A plasma half-life ($t_{1/2}$) of 2.3 hours was determined after single oral dose of 580 mg/kg in Sprague-Dawley rats. The highest plasma concentration was reached after 6 hours (Tmax). After a single 6-hour inhalation exposure, $t_{1/2}$ of 2.92 and 4.91 hours were determined at the exposure concentrations of 2.41 and 5.16 mg/L, respectively, in rats. The Tmax was determined to be 0.5 hour for both exposure concentrations. No additional information was identified for elimination.
- In summary, oral and inhalation absorption of diacetone alcohol is rapid and complete, while dermal absorption is low, and was less than 5% after 24 hours of exposure. The physicochemical properties of diacetone alcohol indicates that it is expected to be evenly distributed throughout the body. No information is available on its metabolism. Based on limited oral and inhalation toxicokinetic studies in rats, diacetone alcohol is expected to be rapidly excreted.

Hazard Classification Summary

<u>Group I Human Health Effects (Group I Human)</u>

Carcinogenicity (C) Score (H, M, or L): *M*
Diacetone alcohol was assigned a score of Moderate for carcinogenicity based on limited evidence of carcinogenicity seen in two carcinogenicity studies with the surrogate methyl isobutyl ketone following repeated inhalation exposure, which led ECHA to classify the surrogate to GHS Category 2. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals (CPA 2018b). Confidence is low as it is based on a weak surrogate (due to the slow metabolism rate of methyl isobutyl ketone to diacetone alcohol).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
    - *Inhalation: <u>Surrogate: Methyl isobutyl ketone (CAS #108-10-1)</u>:* In a GLP-compliant carcinogenicity study conducted according to OECD Guideline 451, male and female F344/N rats (50/sex/dose) were exposed to 1,847, 3,695, or 7,398 mg/m^3 methyl isobutyl ketone (vapor) (equivalent to 1.847, 3.695, and 7.398 mg/L) for 6 hours per day, 5 days per week for 2 years. High dose males had decreased survival and increases in renal adenomas and adenomas or carcinomas (combined). The authors noted the increase in renal tumors

may be due to chronic progressive nephropathy and α-2μ-globulin related mechanism, which is not considered relevant to humans. Two high dose females had renal mesenchymal tumors. A significant increase in mononuclear cell leukemias was reported in high dose male rats. The authors reported an exposure-related increase in benign or malignant pheochromocytoma (combined) of the adrenal gland in male rats. They noted that the increase in pheochromocytomas was within the historical range for chamber controls from inhalation studies; however, the incidence in high dose males was at the upper limit (Klimisch 2, reliable with restrictions).

- *Inhalation: Surrogate: Methyl isobutyl ketone (CAS #108-10-1)*: In a GLP-compliant carcinogenicity study conducted according to OECD Guideline 451, male and female B6C3F1 mice (50/sex/dose) were exposed to 1,843, 3,683, or 7,341 mg/m^3 methyl isobutyl ketone (vapor) (equivalent to 1.843, 3.683, and 7.341 mg/L) for 6 hours per day, 5 days per week for 2 years. Treatment produced a concentration-related increase in multiple adenomas in male and female mice. High dose male and female mice had increased hepatocellular adenomas, and adenomas or carcinomas (combined). The authors noted that methyl isobutyl ketone may induce cytochrome P450 enzymes following activation of the mouse constitutive androstane receptor (CAR) in a manner similar to phenobarbital-like compounds. They reported that activation of CAR is not relevant to humans (Klimisch 2, reliable with restrictions).

- ECHA 2018a, 2019
  - *Surrogate: Methyl isobutyl ketone (CAS #108-10-1)*: The carcinogenicity of methyl isobutyl ketone was evaluated by ECHA and the Committee for Risk Assessment (RAC) who concluded that methyl isobutyl ketone has a carcinogenic potential relevant for humans. Although liver tumors seen in mice appeared to be not relevant for humans as they were CAR-mediated, mechanistic tests in human cells were missing. In terms of the kidney tumors seen in male rats which were partially due to an α2μ-globulin related mechanism not relevant to humans, there was also some kidney toxicity seen in female mice which indicated that another mechanism may also be involved in the tumor formation. A recent review identified some uncertainties regarding the link between α2μ and kidney tumor formation. Tumors were also seen at other sites (renal mesenchymal tumors, adrenal gland, leukemia), but were restricted to one sex and one species and were only slightly above or in the upper range of historical control data. Based on the limited evidence of carcinogenicity in animal studies, ECHA and RAC proposed a GHS Carcinogenicity Category 2 classification for methyl isobutyl ketone (H351: Suspected of causing cancer). Carcinogenesis is proposed to occur through a non-genotoxic mechanism.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Diacetone alcohol was assigned a score of low for mutagenicity/genotoxicity based on negative results in *in vitro* mutagenicity and clastogenicity assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *In vitro*: In a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471, *Salmonella typhimurium* test strains TA98, TA100, TA1535, and TA1537, as

well as *Escherichia coli* strain WP_2 *uvr*A, were tested at concentrations of 313-5,000 µg/plate diacetone alcohol (99.8% purity) in water with and without metabolic activation. S9 metabolic activation mix was derived from rat liver induced with phenobarbital and 5,6-benzoflavone. Positive and vehicle controls were used; however, the specific chemicals used were not identified. No cytotoxicity was observed and positive and vehicle controls were valid. No mutagenic activity was observed under the conditions of this study (Klimisch score 1, reliable without restriction).

- *In vitro*: In a non-GLP compliant bacterial reverse mutation assay conducted according to OECD Guideline 471, *S. typhimurium* test strains TA98, TA100, TA1535, TA1537, and TA1538 were tested at concentrations of 100-10,000 µg/plate diacetone alcohol (purity not reported) in water with and without metabolic activation. S9 metabolic activation mix was derived from Aroclor 1254-induced rodent liver microsomes. Positive and vehicle controls were used; however, the specific chemicals used were not identified. No cytotoxicity was observed and positive and vehicle controls were valid. No mutagenic activity was observed under the conditions of this study (Klimisch score 2, reliable with restriction).
- *In vitro*: In a non-GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471, *S. typhimurium* test strains TA98, TA100, TA1535, and TA1537, as well as *E. coli* strain WP_2 *uvr*A, were tested at concentrations of 31.25-4,000 µg/plate diacetone alcohol (purity not reported) in water with and without metabolic activation. Details about the S9 metabolic activation mix, as well as positive and negative controls were not provided. No cytotoxicity was observed and positive and vehicle controls were valid. No mutagenic activity was observed under the conditions of this study (Klimisch score 2, reliable with restriction).
- *In vitro*: In a GLP-compliant mammalian cell mutation assay conducted according to OECD Guideline 476/EU method B.17, mouse lymphoma L5178Y cells were tested at concentrations of 156.3-5,000 µg/mL diacetone alcohol (99.7% purity) in RPMI culture medium, with and without metabolic activation. Details about the S9 metabolic activation mix were not provided. Positive controls with and without metabolic activation were cyclophosphamide and methylmethane sulfonate, respectively. Under the conditions of the study, diacetone alcohol did not cause a significant increase in mutations at the thymidine kinase locus (Klimisch 1, reliable without restrictions).
- *In vitro*: In a non-GLP compliant mammalian cell mutation assay conducted according to OECD Guideline 476, mouse lymphoma L5178Y cells were tested at concentrations of 3,000-5,000 µg/mL diacetone alcohol (99.7% purity) in water, with and without metabolic activation. S9 metabolic activation mix was derived from Aroclor 1254-induced rodent liver microsomes. Positive controls with and without metabolic activation were not specified. Under the conditions of the study, diacetone alcohol did not cause a significant increase in mutations at the thymidine kinase locus (Klimisch 2, reliable with restrictions).
- *In vitro*: In a mammalian chromosomal aberration assay, conducted in accordance with OECD Guideline 473 (GLP compliance not reported), Chinese hamster lung (CHL/IU) cells were tested at concentrations of exposed to the test substance at concentrations of 0.3-1.2 mg/mL diacetone alcohol (purity not reported) in water, with and without metabolic activation. S9 metabolic activation mix was derived from rat liver induced with phenobarbital and 5,6-benzoflavone. Positive controls with and without metabolic activation were cyclophosphamide and mitomycin C, respectively. Under the conditions of the study, diacetone alcohol did not induce a significant increase in the number of cells with chromosome aberrations (Klimisch score 1, reliable without restrictions)**.**
- *In vitro*: In a mammalian chromosomal aberration assay, conducted in accordance with OECD Guideline 473 (GLP compliance not reported), RL4 rat liver cells were tested at

concentrations of exposed to the test substance at concentrations of 750-4,000 µg/L diacetone alcohol (purity not reported) in water, without metabolic activation. Positive controls with and without metabolic activation were 7,12-dimethylbenzanthracene and water, respectively. Under the conditions of the study, diacetone alcohol induced a slight increase in chromatid damage, breaks and fragments but there was no dose-response (Klimisch score 2, reliable with restrictions)**.** *The result was judged to be negative by the European Food Safety Authority (EFSA 2004).*

Reproductive Toxicity (R) Score (H, M, or L): L

Diacetone alcohol was assigned a score of Low for reproductive toxicity based on a lack of reproductive effects in a GLP-compliant reproductive/developmental toxicity screening study (OECD 421) and an extended one-generation reproductive toxicity study (OECD 443) in rats. The reproductive effects seen in the OECD 422 combined repeated dose and reproductive/developmental toxicity screening study are most likely not toxicologically meaningful because they were not statistically significant and not found in the more recent studies that included sufficient evaluation of reproductive toxicity related endpoints. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and they are not classified under GHS (CPA 2018b). Confidence is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan – GHS: H361 (Toxic to reproduction – Category 2)
- UNEP 2000, ECHA 2023a
  - *Oral:* In a GLP-compliant combined repeat dose and reproductive/developmental toxicity screening test conducted according to OECD Guideline 422, SD (Crj: CD) rats received the test substance (purity 99.85%) at 0, 30, 100, 300, or 1,000 mg/kg/day by gavage for 44 days (males) or 41-45 days (females, from 14 days before mating to day 3 of lactation). Reproductive toxicity was found only at the highest dose: a tendency for decreased fertility index, number of implantations and implantation index. Maternal toxicity was also reported in treated animals at the high dose (reduced weight gain, increased relative kidney, liver, and adrenal weights with histopathological lesions). Although not all the changes in the reproductive performance are statistically significant and may have been secondary to maternal toxicity, the document/authors established the NOAEL and LOAEL at 300 and 1,000 mg/kg/day for reproductive toxicity for this study (Klimisch score 2, reliable with restrictions).
  - *Oral:* In a GLP-compliant reproduction/developmental toxicity screening test conducted according to OECD Guideline 421 as a preliminary study to the extended one generation study, male and female Sprague-Dawley rats (10/sex/dose) were administered diacetone alcohol (99.85% purity) in corn oil daily by gavage at doses of 0, 50, 250, or 750 mg/kg/day. Male rats were exposed for 28 days and toxicity phase females were exposed for 56 days. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, testes and epididymis weights, sperm measurement, uterine content, reproductive indices (copulation index, fertility index, delivery index, viability index, number of corpora lutea, and number of implantation), and histopathology. Offspring were sacrificed on postnatal day (PND) 13 and evaluated for survival, mean litter size, sex ratio, body weight, and external and internal abnormalities. Statistical analysis was performed and authors stated that a probability value of $p < 0.05$ (two tailed) was used as the critical level of significance. Treatment caused transient decrease in body weight gain and decrease in food consumption ($p<0.05$) and adverse effects on kidneys in males examined

microscopically at 750 mg/kg/day. There were no treatment-related effects on any of the reproductive parameters measured. Authors assigned a NOAEL of 750 mg/kg/day for reproductive toxicity. The systemic toxicity NOAEL was 250 mg/kg/day (Klimisch score 1, reliable without restriction).

- *Oral:* In a GLP-compliant extended one generation reproductive toxicity study conducted according to OECD Guideline 443, male and female Sprague-Dawley rats (25/sex/dose for F0) were administered the test substance (99.68% purity) in corn oil daily by gavage at doses of 0, 50, 200, or 600 mg/kg during a premating period of 2 weeks and during mating and gestation. For male animals, the administration continued for at least 10 weeks (68-72 days). Treatment of females continued throughout the mating, gestation, and lactation periods up to PND 21. At weaning, pups were distributed to two cohorts, 1A and 1B. Pups of Cohort 1A (20/sex/dose) were given the test item for at least 10 weeks and then sacrificed (13/14 weeks of nominal age). Pups of Cohort 1B (20/sex/dose) were given the test item for at least 10 nominal weeks before pairing, and then animals were mated. Treatment of Cohort 1B males continued during the mating period for up to 17 nominal weeks. Treatment of Cohort 1B females continued during the mating period, gestation of F2 litters, and up to PND 21/22. F0 and Cohort 1A and 1B adults were evaluated for mortality, clinical signs (including neurotoxicity assessment), body weight, food consumption, estrous cycle, mating performance (F0 and Cohort 1B only), clinical pathology (hematology/coagulation, clinical chemistry, and urinalysis), blood hormone levels (adult animals and pups for F0, adult only for Cohort 1A, and adult and F2 pups for Cohort 1B), anogenital distance on PND 1 (F0 and Cohort 1B F2 pups), litter data (F0 and Cohort 1B only), macroscopic observations, and organ weights. Histopathology examinations were limited to enumeration of ovarian follicles and corpora lutea in control and high dose groups, and liver and kidney of all treated males in F0 and Cohort 1A. Treatment caused adverse kidney effects in male rats at 600 mg/kg/day. In terms of fertility and reproductive performance parameters, no treatment-related effects were found on estrous cycle, epididymal and testicular sperm parameters, and reproductive performance of adult male and female animals of the F generation and of Cohorts 1A and 1B. Further, no differences in reproductive indices including fertility index were seen between the control and treated groups from both generations. Accordingly, the authors established a NOAEL of 600 mg/kg for fertility and reproductive performance of F0, F1 and F2 generation animals, which was the highest dose tested (Klimisch score 1, reliable without restriction).

- NITE 2009
  - Diacetone alcohol is classified to GHS Category 2 for reproductive toxicity (H361) by the GHS-Japan list based on the results from the OECD Guideline 421 study. The results from the other two reproductive toxicity studies with diacetone alcohol described above were not considered in the GHS-Japan evaluation as they became available in 2019, after Japan's assessment date (NITE 2009). *Therefore, ToxServices weighed more heavily the results from the most recent studies, which were of high quality and included sufficient evaluation of the reproductive toxicity related parameters.*

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): M
Diacetone alcohol was assigned a score of Moderate for developmental toxicity based on ToxServices classifying it as a GHS Category 2 developmental toxicant. Diacetone alcohol caused fetal malformations in rabbit pups when tested in an OECD 414 developmental toxicity study. Increased prenatal and/or postnatal deaths and/or decreased offspring body weights were also measured in rats in the presence of maternal systemic toxicity. According to GreenScreen® criteria association with the

authoritative MAK: Pregnancy Risk Group D list warrants a Low, Moderate, or High score. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when they correspond to a GHS Category 2 developmental toxicity classification (CPA 2018b). Confidence is high as it is based on experimental data of good quality for the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* MAK – Pregnancy Risk Group D
- UNEP 2000, ECHA 2023a
    - *Oral:* In the previously described combined repeat dose and reproductive/developmental toxicity screening test performed according to OECD Guideline 422, SD (Crj: CD) rats received the test substance at 0, 30, 100, 300, or 1,000 mg/kg/day by gavage for 44 days (males) or 41 – 45 days (from 14 days before mating to day 3 of lactation, females). Developmental toxicity was reported only at the highest dose: a tendency for decreased number of pups born, delivery index, live birth index, number of pups alive and viability on lactation day 4. Although not all the changes are statistically significant and may have been secondary to maternal toxicity, the document/authors established the NOAEL and LOAEL at 300 and 1,000 mg/kg/day for developmental toxicity (Klimisch score 2, reliable with restrictions).
    - *Oral:* In the previously-described GLP-compliant reproduction/developmental toxicity screening test conducted according to OECD Guideline 421 as a preliminary study to the extended one-generation study, male and female Sprague-Dawley rats (10/sex/dose) were administered diacetone alcohol (99.85% purity) in corn oil daily by gavage at doses of 0, 50, 250, or 750 mg/kg/day. Treatment caused progressive decrease in pups' survival at the high dose (750 mg/kg/day) during the lactation period (sacrificed on PND 13). In addition, a statistically significant decrease in body weight was measured in pups at the high dose from PND1 to PND13, reaching statistical significance on PND 4 (litter weight) and PND 13 (litter and mean pup weights). Based on these findings, authors assigned a NOAEL of 250 mg/kg/day for pup development (Klimisch score 1, reliable without restriction).
    - *Oral:* In the previously described GLP-compliant extended one-generation reproductive toxicity study conducted according to OECD Guideline 443, male and female Sprague-Dawley rats (25/sex/dose for F0) were administered diacetone alcohol (99.68% purity) in corn oil daily by gavage at doses of 0, 50, 200, or 600 mg/kg during a premating period of 2 weeks and during mating and gestation until weaning at PND 21. At weaning, pups were distributed to two cohorts, 1A and 1B. Pups of Cohort 1A (20/sex/dose) were given the test item for at least 10 weeks and then sacrificed (13/14 weeks of nominal age). Pups of Cohort 1B (20/sex/dose) were given the test item for at least 10 nominal weeks before pairing, and then animals were mated to produce F2 litters. Treatment of Cohort 1B males continued during the mating period up to 17 nominal weeks. F1 offspring survival was reduced at the dose level of 600 mg/kg/day, but remained within the reference control range and not statistically significant. This was also evident at the same dose level in F2 litters with slightly reduced survival on PND 1 and PND 4 when compared to the control group. However, pup survival was significantly reduced only on PND 4. Therefore, since the change measured in F1 pups was still evident in F2 pups and was more pronounced, the relation with the test item cannot be excluded. Accordingly, authors assigned a NOAEL of 200 mg/kg/day for developmental toxicity (Klimisch score 1, reliable without restriction).
    - *Oral:* In a GLP-compliant developmental toxicity study conducted according to OECD Guideline 414, pregnant female Sprague-Dawley rats (24/dose) were administered oral doses of diacetone alcohol (>99% purity) at 0, 100, 300, or 1,000 mg/kg in corn oil on gestation

days 6 to 20 via gavage. Treatment did not alter the pregnancy duration, numbers of corpora lutea, implantations, live fetuses, resorptions, or post-implantation losses. No statistically significant adverse effects were reported on litter size, sex ratio, fetal body weights, or external, soft tissue, head, and skeletal malformations. The authors identified a developmental NOAEL of 1,000 mg/kg/day, which was the highest dose tested (Klimisch score 1, reliable without restriction).

- *Oral:* In a GLP-compliant developmental toxicity study conducted according to OECD Guideline 414, pregnant female New Zealand White rabbits (24/dose) were administered oral doses of diacetone alcohol (>99% purity) at 0, 100, 300, or 800 mg/kg in water on gestation days 6 to 28 via gavage. Treatment caused external (head and abdominal closure defects), visceral (malformed aortas), and skeletal (split frontal) malformations in pups of females receiving 800 mg/kg/day (statistics not performed on these effects). Further, two pups at 300 mg/kg/day showed malformed aortas. Accordingly, authors identified a developmental NOAEL of 100 mg/kg/day. The maternal toxicity NOAEL was considered to be 300 mg/kg/day based on the effects on body weight change and food consumption having led to the premature euthanasia of one female at 800 mg/kg/day (Klimisch score 1, reliable without restriction).
- Based on the results from the above studies, authors of the REACH dossier for diacetone alcohol classified it to GHS Category 2 for development toxicity with a hazard statement of H361d: Suspected of damaging the unborn child.

Endocrine Activity (E) Score (H, M, or L): *M*

Diacetone alcohol was assigned a score of Moderate for endocrine activity based on significant weight increase and histopathological changes in the adrenals of male and female rats following repeated oral exposure at doses of 300 mg/kg/day and above. However, there are no carcinogenicity, reproductive/ developmental toxicities, and/or repeated dose toxicities found that could be attributed to endocrine mode of action. Even if they were attributed to endocrine disruption, the score for this endpoint would not be raised to High because the scores for these other endpoints are at most Moderate. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity, and the score is raised to High only when there is linked health effects leading to High scores for those respective endpoints (CPA 2018b). Confidence is low due to lack of study details on the weight and histopathology examination of the adrenal glands in the OECD Guideline 443 study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral:* In the previously described combined repeat dose and reproductive/developmental toxicity screening test conducted according to OECD Guideline 422, SD (Crj: CD) rats received the test substance at 0, 30, 100, 300 or 1,000 mg/kg/day by gavage for 44 days (males) or 41 – 45 days (from 14 days before mating to day 3 of lactation, females). Treatment caused significant increases in the absolute (21%) and relative (24%) weights of the adrenals in males at 1,000 mg/kg/day. In addition, vacuolization of the cells of the zona fasciculata in the adrenals was noted in one male in the 300 mg/kg group, and five males and three females in the 1,000 mg/kg group. While REACH dossier authors established a NOAEL of 100 mg/kg/day and LOAEL of 300 mg/kg/day, the basis of this assignment seems to be mainly based on kidney toxicity in females (Klimisch 2, reliable with restriction).
  - *Oral:* In a GLP-compliant repeated dose toxicity study conducted according to OECD

Guideline 408, Sprague-Dawley rats (15/sex/high-dose, 10/sex/low- and mid-doses) were administered diacetone alcohol in corn oil by gavage at doses of 0, 25, 100, and 600 mg/kg/day for 90 days. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, organs weight, gross pathology, and histopathology. Statistical analysis was performed and authors stated that a probability value of $p < 0.05$ (two tailed) was used as the critical level of significance. The mean absolute and relative weights of the adrenal glands were statistically significantly increased (+26% and +38%, respectively) in males at 600 mg/kg/day. There was also minimal to moderate vacuolation of cortical cells (mostly in the zona fasciculata) in the adrenals of males at 25 mg/kg/day (3/10) and 600 mg/kg/day (4/10), but not at 150 mg/kg/day. This finding was not reversed at the end of treatment-free period. Given the lack of dose correlation and the low amplitude in most of the animals, authors considered this finding as incidental. Furthermore, in the highest dose groups lower mean epididymal sperm counts (-10 %) and lower number of estrus cycles (not statistically significant, 2.4 vs 3.5) and cycle length (4.7 vs 7.8 days of control) were measured (Klimisch score 1, reliable without restriction). *ECHA considered these changes to be associated with endocrine-disrupting modes of action of the registered substance (ECHA 2018b).*

- *Oral:* In the previously described GLP-compliant extended one generation reproductive toxicity study conducted according to OECD Guideline 443, male and female Sprague-Dawley rats were (25/sex/dose for F0) were administered the test substance (99.68% purity) in corn oil daily by gavage at doses of 0, 50, 200, and 600 mg/kg during a premating period of 2 weeks and during mating and gestation. The study included evaluation of endocrine related parameters as verified in the EFSA Guidance for the identification of endocrine disruptors (EFSA 2018a). These were estrous cycle, spermatogenic cycle, nipple check, anogenital distance (AGD) and histopathological examination of testes, epididymides, ovaries, uterus, and thyroid. There were no adverse effects on any of these parameters. However, authors did not report data on the weight and histopathology examination of the adrenal glands, which were the critical endocrine related effects seen in the prior studies (Klimisch score 1, reliable without restriction).

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L

Diacetone alcohol was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values of > 2,000 mg/kg (rats). GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are > 2,000 mg/kg and inhalation vapor LC_{50} values are greater than 20 mg/L/4 hr (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral:* LD_{50} = 3,002 mg/kg in male and female Wistar rats (non-GLP, OECD Guideline 401) (Klimisch 2, reliable with restrictions).
  - *Oral:* LD_{50} = 4,000 mg/kg in male Sherman rats (non-GLP, OECD Guideline 401)

(Klimisch 2, reliable with restrictions).
- *Dermal:* LD_{50} > 1,875 mg/kg in male and female Wistar rats (non-GLP, OECD Guideline 204) (Klimisch 2, reliable with restrictions).
- *Dermal:* LD_{50} = 14.5 mL/kg[9] in rabbits (sex and strain not reported) (non-GLP, standard acute method) (Klimisch 2, reliable with restrictions).
- *Inhalation:* LC_0 (vapor) > 7.6 mg/L/4 hr in male and female Wistar rats (non-GLP, OECD Guideline 403) (Klimisch 2, reliable with restrictions).

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): *H*

Diacetone alcohol was assigned a score of High for systemic toxicity (single dose) due to being classified to GHS Category 2 by Japan based on a measured LOAEL of 1,880 mg/kg from an oral acute toxicity study. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (single dose) when they are classified as GHS Category 2 (CPA 2018b). Confidence is low due to lack of study details on the critical study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS-Japan: Category 2 (blood, liver) (NITE 2009).
    - GHS-Japan: Category 3 (respiratory tract) (NITE 2009).
- ECHA 2023a
  - *Oral*: In a non-GLP acute oral toxicity study conducted in a manner similar to OECD Guideline 401, Wistar rats (6/sex/dose) received diacetone alcohol (purity not reported) as single doses of 1,880, 2,369, 3,002, 3,760, or 5,969 mg/kg by gavage. An observation period of 14 days followed. Within a few hours of dosing, treated animals exhibited signs of lethargy and showed piloerection; one day later they were ataxic and at the higher dose levels, comatose. One male and one female at 2,369 mg/kg died, and all animals at 3,002 mg/kg and above died. There were no details reported related to body weight and gross pathology. Based on the mortality rate, the authors identified an oral LD_{50} value of 3,002 mg/kg, with 95% confidence limits of 2,738-3,290 mg/kg (Klimisch 2, reliable with restrictions).
  - *Dermal*: In a non-GLP acute dermal toxicity study conducted in a manner similar to OECD Guideline 402, undiluted diacetone alcohol was applied to the shaved dorsal skin of Wistar rats (6/sex/dose) at 2 mL/kg (equivalent to 1,875 mg/kg as calculated by the study authors) for 24 hours. The animals were observed for signs of toxicity for 14 or 21 days and then necropsy was performed. There were no mortalities, reactions, or clinical signs of toxicity. There were no details reported related to body weight and gross pathology. Authors identified a dermal LD_{50} of greater than 1,875 mg/kg body weight (Klimisch 2, reliable with restrictions).
  - *Inhalation*: In a non-GLP acute inhalation toxicity study conducted in a manner similar to OECD Guideline 403, Wistar rats (5/sex/dose) were exposed to diacetone alcohol vapor at a concentration of 7.6 mg /L (range 7.2 to 8.1 mg/L) for 4 hours via whole-body exposure. The animals were observed for 14 days after exposure. No animals died, and no adverse effects were reported during exposure or during the 14-day observation period. Authors identified an inhalation LC_{50} of greater than 7.6 mg/L (Klimisch 2, reliable with restrictions).
  - Diacetone alcohol caused respiratory tract irritation following a 15-minute exposure to 483

[9] Equivalent to 13.63 g/kg, based on a density of 0.94 g/cm^3.

mg/m^3 in 12 human volunteers. *Based on the data from human study, diacetone alcohol is classified in its REACH registration dossier as a respiratory irritant (STOT SE Category 3) with a hazard statement of H335: May cause respiratory irritation.*

- NITE 2009
    - Diacetone alcohol is classified to GHS Category 2 for systemic toxicity following single exposure with a hazard statement of H371: may cause damage to organs (blood, liver) by the GHS-Japan list. The basis of the classification is the acute oral toxicity study described above in which rats exposed to 2 mL/kg (1,880 mg/kg) diacetone alcohol by gavage showed liver damage (increased numbers of lymphocytes, followed by cloudy swelling, vacuolization, and granulation of the cytoplasm) and effects on the blood system. *These details were not provided or reported in the REACH registration dossier of diacetone alcohol or in its OECD SIDS assessment, and therefore ToxServices could not verify the results.*
    - Diacetone alcohol is also classified to GHS Category 3 for respiratory irritation by the GHS-Japan list based on the above data in humans.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): L

Diacetone alcohol was assigned a score of Low for systemic toxicity (repeated dose) based on an oral NOAEL of 600 mg/kg/day from a 90-day study supported by lack of systemic adverse effects in other oral and inhalation repeated dose toxicity studies with shorter or similar duration at doses greater than the guidance values. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when they are not classified under GHS based on oral and inhalation LOAEL values >100 mg/kg/day and 1 mg/L/6 hr/day (vapor), respectively, for 90-day studies (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
    - *Oral*: In the previously described combined repeat dose and reproductive/developmental toxicity screening test conducted according to OECD Guideline 422, SD (Crj: CD) rats received the test substance at 0, 30, 100, 300 or 1,000 mg/kg/day by gavage for 44 days (males) or 41-45 days (from 14 days before mating to day 3 of lactation, females). Females at the highest dose had decreased body weight gain before mating, with one female sacrificed before the end of the study due to difficulty in delivery. Hematological examinations revealed increased platelet count, GOT, total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine and calcium, and decreased glucose in males at the highest dose. Histopathological examination of kidneys showed increased deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg/day or higher, basophilic tubules at doses of 300 mg/kg/day and higher, and dilatation of the distal tubules at the highest dose. In the kidneys of females, there were slight (not significant) increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium at 300 and 1,000 mg/kg/day. At the highest dose, there was also hepatocellular hypertrophy in both sexes. The document/authors established the NOAELs at 30 mg/kg/day (LOAEL = 100 mg/kg/day) for males and 100 mg/kg/day for females (LOAEL = 300 mg/kg/day) (UNEP 2000). As hyaline droplets nephropathy in male rats are associated with alpha-2µ-globulin nephropathy, and therefore not relevant to humans, ECHA established the overall NOAEL and LOAEL at 100 and 300 mg/kg/day, respectively, based on kidney effects in females

(Klimisch 2, reliable with restrictions). *The LOAEL of 300 mg/kg/day is above the duration-adjusted GHS guidance values of 200 mg/kg/day*[10] *(oral) for Category 2 for a 45-day study. However, the NOAEL of 100 mg/kg/day is below the duration-adjusted GHS guideline values for Category 2 (20-200 mg/kg/day). Therefore, there are insufficient data to determine if adverse effects would occur at 200 mg/kg/day.*

- *Oral:* In a GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 408, Sprague-Dawley rats (15/sex/high-dose, 10/sex/low- and mid-doses) were administered diacetone alcohol in corn oil by gavage at doses of 0, 25, 100, 600 mg/kg/day for 90 days. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, organs weight, gross pathology, and histopathology. There were no treatment-related effects on clinical signs, body weight, estrous cycles, sperm analysis and clinical pathology parameters. There were no effects on food consumption. However, at the high dose level (600 mg/kg/day) treatment caused non-adverse changes in the liver consisting of increased weight associated with hepatocellular hypertrophy, in both sexes. Further, in males only, non-adverse findings were also found in the kidneys from 25 mg/kg/day and were characterized by increased weights and tubular hyaline droplet accumulation (as confirmed by immunohistochemistry), frequently associated with tubular basophilia and granular casts. These kidney changes were considered specific to male rats and non-relevant to humans. As a result, authors established a NOAEL of 600 mg/kg/day; which was the highest doses tested due to the lack of adverse effects (Klimisch 1, reliable without restrictions). *The NOAEL of 600 mg/kg/day is above the GHS threshold value of 100 mg/kg/day (oral) for Category 2 for a 90-day study. Therefore, diacetone alcohol is not classified per GHS.*
- *Oral:* In the previously described GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening conducted according to OECD Guideline 421 as a preliminary study to the extended one generation study, male and female Sprague-Dawley rats (10/sex/dose) were administered diacetone alcohol (99.85% purity) in corn oil daily by gavage at doses of 0, 50, 250 or 750 mg/kg/day. Male rats were exposed for 28 days and toxicity phase females were exposed for 56 days. Statistical analysis was performed and authors stated that a probability value of $p < 0.05$ (two tailed) was used as the critical level of significance. Treatment caused transient decrease in body weight gain of females at all doses, a statistically significant decrease in food consumption of females at the high dose ($p<0.05$) and adverse effects on kidneys in males examined microscopically at 750 mg/kg/day. Accordingly, authors assigned a systemic toxicity NOAEL of 250 mg/kg/day based on decreased food consumption in females at the high dose. Kidney effects in males are confounded by the α2μ-globulin mechanism that is not relevant to humans (Klimisch 1, reliable without restriction). *As the critical effects is based on effects in females, the exposure duration of treated females were used as basis for the classification purposes. The LOAEL of 750 mg/kg/day in females is above the duration-adjusted GHS guidance values of 161mg/kg/day*[11] *(oral) for Category 2 for a 56-day study. The NOAEL of 250 mg/kg/day is also above the duration-adjusted GHS guideline values for Category 2 (161 mg/kg/day). Therefore, diacetone alcohol is not classified under GHS.*
- *Oral:* In the previously described GLP-compliant extended one generation reproductive toxicity study conducted according to OECD Guideline 443, male and female Sprague-Dawley rats were (25/sex/dose for F0) were administered the test substance (99.68% purity) in corn oil daily by gavage at doses of 0, 50, 200 and 600 mg/kg during a premating period

[10] 100 mg/kg/day x 90 days/45 days = 200 mg/kg/day
[11] 100 mg/kg/day x 90 days/56 days = 161 mg/kg/day

of 2 weeks and during mating and gestation. For male animals, the administration continued for at least 10 weeks (68-72 days). Treatment of females continued throughout the mating, gestation and lactation periods up to Day 21 post-partum. At weaning, pups were distributed to two cohorts, 1A and 1B. Pups of Cohort 1A (20/sex/dose) were given the test item for at least 10 weeks and then sacrificed (13/14 weeks of nominal age). Pups of Cohort 1B (20/sex/dose) were given the test item for at least 10 nominal weeks before pairing, and then animals were mated. Treatment of Cohort 1B males continued during the mating period up to 17 nominal weeks. Treatment of Cohort 1B females continued during the mating period and up to Days 21/22 post-partum. Animals from F0 and Cohort 1A and 1B were evaluated for mortality, clinical signs (including neurotoxicity assessment), body weight, food consumption, estrous cycle, mating performance, clinical pathology (hematology/coagulation, clinical chemistry and urinalysis), hormone levels (adult animals and pups), anogenital distance, litter data, macroscopic observations and organ weights. Treatment caused adverse kidneys effects in male rats at 600 mg/kg/day. Study authors therefore assigned a NOAEL of 200 mg/kg/day for male rats based on kidney effects, and a NOAEL of 600 mg/kg/day for female rats based on the lack of adverse effects found. As the kidney effects in males are confounded by the male rat-specific α2μ-globulin mechanisms, ToxServices considered the NOAEL of 600 mg/kg/day in females to be the overall NOAEL for human relevant effects (Klimisch 1, reliable without restriction). *As the exposure duration is approximately 13 weeks or longer, ToxServices compared the NOAEL of 600 mg/kg/day to the non-adjusted subchronic GHS guidance value of 100 mg/kg/day. Therefore, diacetone alcohol is not classified under GHS.*

- *Inhalation*: In a 6-week whole body inhalation toxicity study conducted in a manner similar to OECD Guideline 412, Wistar rats (12/sex/dose) received the test substance (purity 99.44%) at concentrations of 0.233, 1.041 or 4.685 mg/L for 6 h/day, 5 days/week for 6 weeks. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, organs weight, gross pathology, and histopathology. At the high dose, there were slight lethargy during and after exposure, reduced body weight gains and increased plasma LDH in females, and increased liver and kidney weights. Histologic changes in the kidney proximal tubules were reported in males. At the mid dose, only liver weight was increased but not accompanied by any histopathological changes. Therefore, the document/authors established a NOAEC of 4.685 mg/L and a NOEC of 1.041 mg/L based on liver weight changes not associated with histological alterations and probably secondary to a metabolic overload and based on the male rat-specific eosinophilic hyaline droplets in the proximal tubular cells as hyaline droplet formation in male rats is not considered to be relevant to human. These doses are equivalent to 0.743 and 3.346 mg/L/6h/day after duration-adjustment (Klimisch 2, reliable with restrictions)[12]. *The NOAEC of 3.852 mg/L/6h/day is above the duration-adjusted GHS guidance values of 2.0 mg/L/6h/day[13] (vapor) for Category 2 for a 6-week study. Therefore, diacetone alcohol is not classified per GHS.*

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): M

Diacetone alcohol was assigned a score of Moderate for neurotoxicity (single dose) based on animal data indicating a transient narcotic effect. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when available data indicate that GHS Category 3 classification is

[12] Converting exposure period 5days/week to daily = 4.685 mg/L x 5 / 7(days) = 3.34 mg/L/day
[13] 1.0 mg/L/6h/day x 90 days/45 days = 2.0 mg/L/6h/day

warranted for transient narcotic effects (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data on the target chemical, supported by a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS-Japan: Category 3 (narcotic effects) (NITE 2009).
- ECHA 2023a
  - *Oral*: In the previously described non-GLP acute oral toxicity study conducted in a manner similar to OECD Guideline 401, Wistar rats (6/sex/dose) received diacetone alcohol (purity not reported) at single doses of 1,880, 2,369, 3,002, 3,760, or 5,969 mg/kg by gavage. Animals were observed for 14 days. Within a few hours of dosing, treated animals exhibited clinical signs of neurotoxicity such as lethargy and piloerection; one day later they were ataxic and at the higher dose levels, comatose (Klimisch 2, reliable with restrictions).
  - *Dermal:* In the previously described acute dermal toxicity study conducted in a manner similar to OECD Guideline 402, undiluted diacetone alcohol was applied to the shaved dorsal skin of Wistar rats (6/sex/dose) at 2 mL/kg (equivalent to 1,875 mg/kg as calculated by the study authors) for 24 hours. The animals were observed for signs of toxicity for 14 or 21 days and then necropsy was performed. There were no mortalities, or clinical signs of neurotoxicity (clinical signs of neurotoxicity often evaluated in animal studies include: drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness, lethargy, and ataxia) (Klimisch 2, reliable with restrictions). *As the dose applied in this study (1,875 mg/kg) is below the GHS cutoff value of 2,000 mg/kg for Category 2, there is insufficient information to conclude that neurotoxicity related adverse effects do not occur at 2,000 mg/kg. Therefore, ToxServices considered the study insufficient for classification purposes.*
  - *Inhalation:* In the previously described acute inhalation toxicity study conducted similarly to OECD Guideline 403, Wistar rats (5/sex/dose) were exposed to diacetone alcohol vapor at a concentration of 7.6 mg /L (range 7.2 to 8.1 mg/L) for 4 hours via whole-body exposure. The animals were observed for 14 days after exposure. No animals died, and no clinical signs of neurotoxicity such as drowsiness, narcosis, lethargy, and ataxia were reported during exposure or during the 14-day observation period (Klimisch 2, reliable with restrictions).
- NITE 2009
  - Diacetone alcohol is classified to GHS Category 3 for narcotic effects following single exposure with a hazard statement of H336: may cause drowsiness or dizziness (narcotic effects) by the GHS-Japan list. The basis of the classification is that inhalation exposure of mice, rats, rabbits, and cats to diacetone alcohol for 1 to 3 hours produced somnolence after a period of restlessness and excitability. The substance was considered primarily a narcotic and anticonvulsant.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L

Diacetone alcohol was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of neurological effects in oral and inhalation repeated dose toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when they are not classified under GHS based on a lack of effects on neurological endpoints below the guidance values of 100 mg/kg/day and 1 mg/L/6h/day (vapor) for 90-day oral and inhalation studies, respectively (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.

    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
    - *Oral*: In the previously described combined repeat dose and reproductive/developmental toxicity screening test conducted according to OECD Guideline 422, SD (Crj: CD) rats received the test substance at 0, 30, 100, 300 or 1,000 mg/kg/day by gavage for 44 days (males) or 41-45 days (from 14 days before mating to day 3 of lactation, females). At the early stage of administration, animals at 300 and 1,000 mg/kg/day had decreased locomotor activity and less response to stimulation by knocking sounds or palpation. No further details were provided (Klimisch 2, reliable with restrictions).
    - *Oral:* In the previously described GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 408, Sprague-Dawley rats (15/sex/high-dose, 10/sex/low and mid-dose) were administered diacetone alcohol in corn oil by gavage at doses of 0, 25, 100, 600 mg/kg/day for 90 days. Neurobehavioral assessment (functional observational battery (FOB), grip strength and locomotor activity) was performed in treated animals at all doses. A dose-related increase in horizontal movements and rearing was measured in males. However, this was not considered an adverse effect due to the absence of correlation at functional observation battery (no signs of hyperactivity or stereotypy) or related clinical signs during the treatment period. No relevant differences were noted at FOB between control and test item-treated groups at the end of the treatment period (Klimisch 1, reliable without restrictions). Accordingly, ToxServices assigned a NOAEL of 600 mg/kg/day for the neurotoxicity, which was the highest dose tested. *The NOAEL of 600 mg/kg/day is above the GHS threshold value of 100 mg/kg/day (oral) for Category 2 for a 90-day study. Therefore, diacetone alcohol is not classified per GHS.*
    - *Oral:* In the previously described GLP-compliant extended one generation reproductive toxicity study conducted according to OECD Guideline 443, male and female Sprague-Dawley rats were (25/sex/dose for F0) were administered the test substance (99.68% purity) in corn oil daily by gavage at doses of 0, 50, 200 and 600 mg/kg during a premating period of 2 weeks and during mating and gestation. For male animals, the administration continued for at least 10 weeks (68-72 days). Treatment of females continued throughout the mating, gestation and lactation periods up to Day 21 post-partum. At weaning, pups were distributed to two cohorts, 1A and 1B. Pups of Cohort 1A (20/sex/dose) were given the test item for at least 10 weeks and then sacrificed (13/14 weeks of nominal age). Pups of Cohort 1B (20/sex/dose) were given the test item for at least 10 nominal weeks before pairing, and then animals were mated. Treatment of Cohort 1B males continued during the mating period up to 17 nominal weeks. Treatment of Cohort 1B females continued during the mating period and up to Days 21/22 post-partum. Animals from F0 and Cohort 1A and 1B were evaluated for neurotoxicity assessment including FOB tests (no details provided). There were no treatment related effects on FOB (Klimisch score of 1, reliable without restriction).
    - *Inhalation*: In the previously described inhalation study, rats received the test substance at 0.232, 1.035, or 4.494 mg/L for 6 hr/day, 5 days/week for 6 weeks (in contrast to UNEP, ECHA indicated the dosing frequency was daily; ToxServices used the 5 days/week frequency as a conservative approach). At the high dose, there was slight lethargy during and after exposure, however animals recovered within a few hours (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Low was assigned. Repeated-dose animal studies indicate that diacetone alcohol causes transient narcotic effects which was captured in the single dose neurotoxicity endpoint. No other adverse effects on the nervous system were reported. Therefore, a score of Low was assigned.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
Diacetone alcohol was assigned a score of Low for skin sensitization based on negative findings in skin sensitization studies. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative, and when they are not classified as per GHS (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - In a GLP-compliant guinea pig maximization test conducted according to OECD Guideline 406, Dunkin-Hartley guinea pigs (10/sex/dose) were intradermally induced with 25% (w/w) diacetone alcohol (purity 99.72%) in a solution of 0.9% w/v of NaCl and with undiluted test material on day 8 and then challenged with undiluted diacetone alcohol (topical) 22 days after the last induction application. No positive reactions were seen and accordingly the test substance was not considered to have sensitizing properties (Klimisch 1, reliable without restrictions).
  - In another guinea pig maximization test that predates GLP but is similar to OECD Guideline 406, the test substance was not sensitizing at 0.5% or undiluted (Klimisch 2, reliable without restrictions).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Diacetone alcohol was assigned a score of Low for respiratory sensitization based on a on lack of structural alerts for respiratory sensitization, negative skin sensitization data and according to ECHA's recommended strategy on evaluation of respiratory sensitization (ECHA 2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative, and they are not classified under GHS (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2022
  - Diacetone alcohol does not contain any structural alerts for respiratory sensitization (Appendix D)
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As diacetone alcohol was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by diacetone alcohol, and as diacetone alcohol does not contain any structural alerts for respiratory sensitization (OECD 2022), diacetone alcohol is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*

Diacetone alcohol was assigned a score of Low for skin irritation/corrosivity based on the results from a high-quality dermal irritation study in rabbits (OECD Guideline 404). GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and support that they are not classified per GHS (CPA 2018b). Confidence is low due to the conflicting reported data on the chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan – GHS: H315 (Skin corrosion/irritation – Category 2).
- ECHA 2023a
  - Diacetone alcohol was minimally irritating in a non-GLP compliant skin irritation study performed according to OECD Guideline 404 in New Zealand White rabbits (3/sex). Diacetone alcohol (500 mg) was applied to intact and abraded rabbit skin under occlusive conditions for 24 hours. Treatment caused very slight transient erythema in animals with abraded skin that was fully reversible by Day 3. The mean score for erythema was 0.16. Treatment caused no irritation in animals with intact skin (Klimisch 2, reliable with restrictions). *According to GHS criteria, a chemical is classified for skin irritation when produce mean scores ≥ 1.5 for erythema and/or edema in at least 2 of 3 animals following readings at 24, 48, and 72 hours (UN 2021). As the irritation score for erythema was less than the guidance value of 1.5, ToxServices did not classify diacetone as a dermal irritant under GHS criteria.*
- NITE 2009
  - Diacetone alcohol is classified to GHS Category 2 for skin irritation (H315) by the GHS-Japan list based on data from a secondary source stating that is moderately irritating in rabbits.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): H

Diacetone alcohol was assigned a score of High for eye irritation/corrosivity based on being associated with EU GHS hazard phrase H319, supported by experimental data. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when associated with EU GHS hazard statement H319, which corresponds to GHS Category 2 (CPA 2018b). The confidence in the score is high as it is based on an authoritative list and reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS: H319 (Serious eye damage/eye irritation – Category 2A).
  - *Screening:*
    - Japan – GHS: H319 (Serious eye damage/eye irritation – Category 2A).
    - Australia – GHS: H319 (Serious eye damage/eye irritation – Category 2A).
    - New Zealand -GHS eye irritation Category 2.
- ECHA 2023a
  - In an ocular irritation test conducted according to OECD Guideline 405 (GLP compliance not specified), 0.1 mL of undiluted diacetone alcohol was instilled into the eyes of 3 rabbits. Treatment caused slight to moderate conjunctival irritation which cleared in 7 days, slight iritis which cleared in 4 days and slight to moderate corneal opacity which cleared in 21 days. The mean individual scores over 24, 48, and 72 hours were 1.3, 1.7, and 1.7 for chemosis, 1.7, 2.3, and 2.0 for conjunctival redness, 0.3, 1.0, and 0.7 for iritis and 1.3, 1.0, and 1.7 for corneal opacity. Based on these results, diacetone alcohol was classified to GHS Category 2 for eye irritation in its REACH registration dossier (Klimisch 2, reliable with

restrictions). *This corresponds to GHS Category 2A as the EU-GHS (CLP) did not adopt Category 2B for eye irritation (EC 2008).*

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L

Diacetone alcohol was assigned a score of Low for acute aquatic toxicity based on measured L/EC_{50} values in fish, daphnia, and algae >100 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when the most conservative L/EC_{50} values are >100 mg/L (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for all three trophic levels for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - 96-hr LC_{50} > 100 mg/L (*Oryzias latipes*, fish) (GLP-compliant, OECD Guideline 203) (Klimisch 1, reliable without restrictions)
  - 48-hr LC_{50} > 1,000 mg/L (*Daphnia magna*, daphnia) (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restrictions)
  - 24-hr EC_{50} = 8,750 mg/L (*D. magna*, daphnia) (non-GLP compliant, OECD Guideline 202) (Klimisch 2, reliable with restrictions)
  - 24-hr EC_{50} = 9,016 mg/L (*D. magna*, daphnia) (non-GLP compliant, ISO 6341) (Klimisch 2, reliable with restrictions)
  - 72-hr EC_{50} > 1,000 mg/L (*Raphidocelis subcapitata*, algae) (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restrictions)
  - 8-hr toxicity threshold concentration (TGK) = 3,000 mg/L (*Scenedesmus quadricauda*, algae) in an algal growth inhibition test (Klimisch 2, reliable with restrictions)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*

Diacetone alcohol was assigned a score of Low for chronic aquatic toxicity based on measured NOEC values >10 mg/L in daphnia and algae. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when the most conservative NOEC values are >10 mg/L (CPA 2018b). The confidence in the score is low as there are no data available for fish.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - 21-day NOEC = 100 mg/L (*D. magna*, daphnia) (GLP-compliant, OECD Guideline 211) (Klimisch 1, reliable without restrictions)
  - 72-hr NOEC > 1,000 mg/L (*R. subcapitata*, algae) (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restrictions)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL

Diacetone alcohol was assigned a score of Very Low for persistence based on water and soil being the dominant environmental compartments and it meeting the 10-day window in a ready biodegradability test. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil,

sediment, and/or water is the dominant environmental compartment and the 10-day window is met (CPA 2018b). The confidence in the score is high as it is based on measured data from a reliable study on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - In a non-GLP compliant ready biodegradation test conducted in a manner similar to OECD Guideline 301A (DOC Die Away Test), activated sludge was exposed to diacetone alcohol at 57.5 mg/L for 28 days. The test substance was totally degraded after 14 days (100%). Accordingly, it was concluded that diacetone alcohol was considered to be readily biodegradable within the 10-day window (Klimisch 2, reliable with restrictions).
- UNEP 2000
  - Readily biodegradable in an OECD Guideline 301C (MITI (I)) test, with 100% degradation after 14 days.
  - Fugacity modeling indicates that if diacetone alcohol is released to the water it is unlikely to distribute to other compartments. However, if it is released into the air or soil, it is likely to distribute to other compartments.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that diacetone alcohol is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 49.3% will partition to water with a half-life of 37.5 days, 48.9% will partition to sediment with a half-life of 75 days, and 0.097% will partition to soil with a half-life of 337.5 days (Appendix E).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

Diacetone alcohol was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of -0.14 and predicted BCFs of up to 0.9318. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} value is no greater than 4 and the BCF value is no greater than 100 (CPA 2018b). The confidence in the score is high as it is based on an experimental log K_{ow}.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017
  - Diacetone alcohol has a measured log K_{ow} of -0.14.
  - BCFBAF predicts a BCF of 0.5 using the regression-based model based on a measured log K_{ow} of -0.14, and a BCF of 0.9318 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix E).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*

Diacetone alcohol was assigned a score of Low for reactivity based on the lack of structural alerts for oxidizing and explosive properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score was low based on the lack of measured data.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of diacetone alcohol. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, diacetone alcohol is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix F).
  - Based on the structure of its components or moieties, diacetone alcohol is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of diacetone alcohol has two oxygens, which are both bonded only to carbon and hydrogen, classification is not warranted.

Flammability (F) Score (vH, H, M, or L): M

Diacetone alcohol was assigned a score of Moderate for flammability based on being classified as a GHS Category 3 or 4 flammable liquid, depending on its acetone impurity content. GreenScreen® criteria classify chemicals as a Moderate hazard for flammability when they are classified as GHS Category 3 or 4 flammable liquids (CPA 2018b). The confidence in the score was high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - Japan – GHS: Flammable liquids – Category 4
    - New Zealand – GHS: Flammable liquids – Category 3
    - Quebec CSST – WHMIS 1988 – Class B3 – Combustible liquids
- ECHA 2023a
  - The flash point of diacetone alcohol with different degrees of purity (acetone content) was examined in a closed-cup method conducted according to EU Method A.9. The flash points of the different samples are:
    - Flash point of diacetone alcohol with analytical purity of 97.96% and acetone content of 1.908% is 42.0°C ± 0.5°C (Klimisch 1, reliable without restriction).
    - Flash point of diacetone alcohol with analytical purity of 98.89% and acetone content of 0.945% is 50.5°C ± 0.5°C (Klimisch 1, reliable without restriction).
    - Flash point of diacetone alcohol with analytical purity of 99.34% and acetone content of 0.493% is 57.0°C ± 0.5°C (Klimisch 1, reliable without restriction).
    - Flash point of diacetone alcohol with analytical purity of 99.85% and acetone content of 0.008% is 63.0°C ± 0.5°C (Klimisch 1, reliable without restriction).
  - *According to GHS Criteria, diacetone alcohol with acetone content of 0.493% and 0.945% is classified as GHS Category 3 flammable liquids (liquids which have a flash point of ≥ 23°C and ≤ 60°C) while diacetone alcohol with acetone content of 0.008% is classified as a GHS Category 4 flammable liquid (liquids which have a flash point of > 60°C and ≤ 93°C).*
- NITE 2009
  - Diacetone alcohol is classified as a flammable liquid (GHS Category 4) by the GHS - Japan list based on a measured flash point of 66°C.
- CCID 2023

- Diacetone alcohol is classified as a flammable liquid (3.1C – medium hazard) by the GHS - New Zealand list based on a measured flashpoint of 56°C obtained from a closed cup method and a boiling point of 168°C.

Use of New Approach Methodologies (NAMs)[14] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for respiratory sensitization, persistence, and bioaccumulation, and *in vitro* testing for genotoxicity. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018b), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

As shown in Table 4, Type I (input data) uncertainties in diacetone alcohol's NAMs dataset include lack of experimental data and validated test methods for respiratory sensitization. Diacetone alcohol's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of diacetone alcohol's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[15]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e. the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[16]

[14] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

[15] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

[16] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE

	The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[17]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	N	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301A Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

[17] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Diacetone Alcohol (CAS #123-42-2)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / Diacetone alcohol / 123-42-2	*M*	L	L	M	*M*	L	*H*	L	M	L	L	*L*	*L*	H	L	*L*	vL	vL	*L*	M

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	Yes	No	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Diacetone alcohol	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

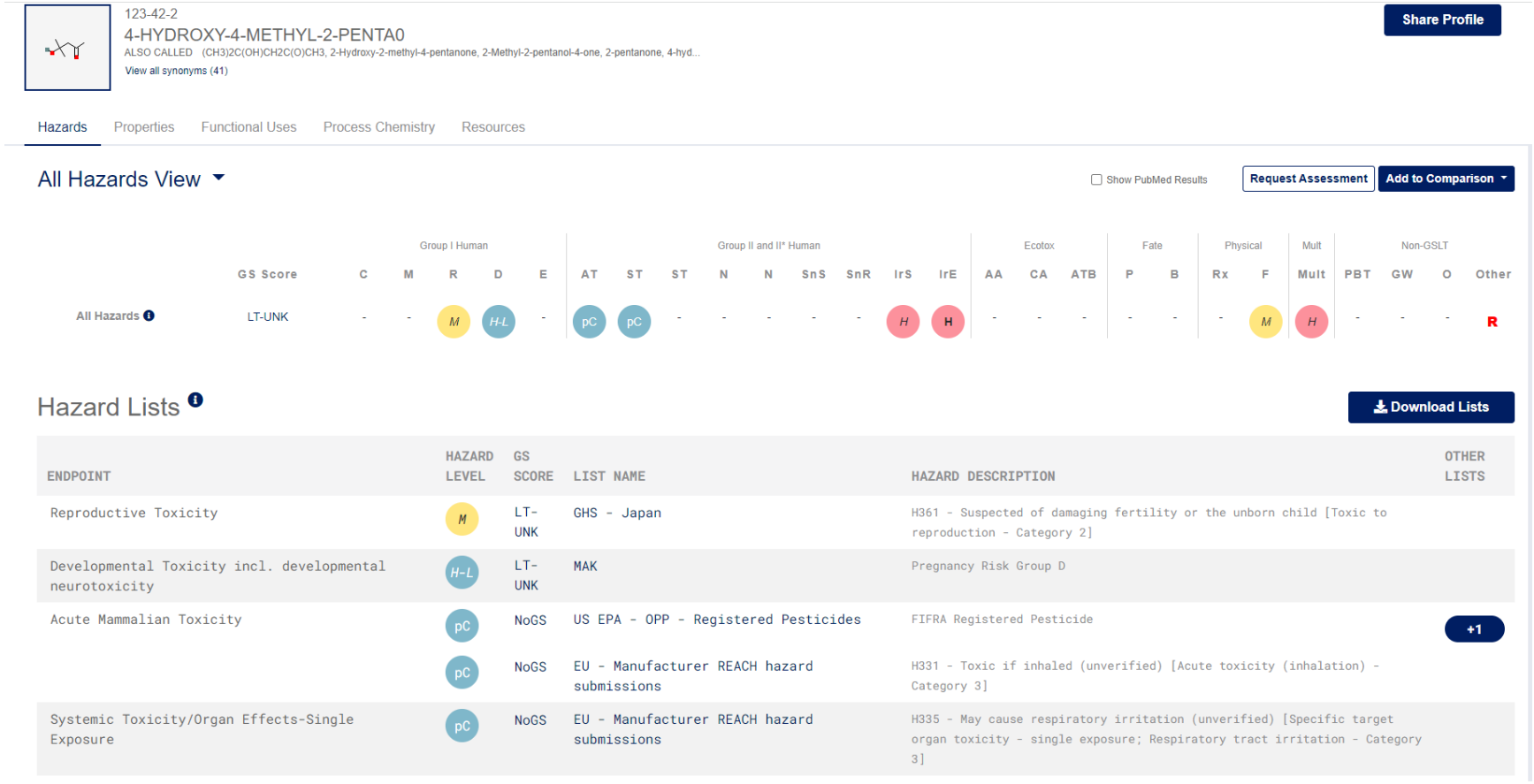
Chemical Name	Final GreenScreen® Benchmark Score
Diacetone alcohol	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for Diacetone Alcohol (CAS #123-42-2)



123-42-2
4-HYDROXY-4-METHYL-2-PENTA0
ALSO CALLED (CH3)2C(OH)CH2C(O)CH3, 2-Hydroxy-2-methyl-4-pentanone, 2-Methyl-2-pentanol-4-one, 2-pentanone, 4-hyd...
View all synonyms (41)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT			
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-UNK	-	-	M	H-L	-	pC	pC	-	-	-	-	-	H	H	-	-	-	-	-	-	M	H	-	-	-	R

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Reproductive Toxicity	M	LT-UNK	GHS - Japan	H361 - Suspected of damaging fertility or the unborn child [Toxic to reproduction - Category 2]	
Developmental Toxicity incl. developmental neurotoxicity	H-L	LT-UNK	MAK	Pregnancy Risk Group D	
Acute Mammalian Toxicity	pC	NoGS	US EPA - OPP - Registered Pesticides	FIFRA Registered Pesticide	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H331 - Toxic if inhaled (unverified) [Acute toxicity (inhalation) - Category 3]	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	

Skin Irritation/Corrosivity	H	LT-UNK	GHS - Japan	H315 - Causes skin irritation [Skin corrosion / irritation - Category 2]	
Eye Irritation/Corrosivity	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	+4
	H	LT-UNK	GHS - Japan	H319 - Causes serious eye irritation [Serious eye damage / eye irritation - Category 2A]	
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Flammability	M	LT-UNK	GHS - Japan	H227 - Combustible liquid [Flammable liquids - Category 4]	+3
	M	LT-UNK	GHS - New Zealand	Flammable liquids category 3	
	M	LT-UNK	Québec CSST - WHMIS 1988	Class B3 - Combustible liquids	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H226 - Flammable liquid and vapour (unverified) [Flammable liquids - Category 3]	
Reproductive and/or Developmental Toxicity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H361 - Suspected of damaging fertility or the unborn child (unverified) [Reproductive toxicity - Category 2]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	Québec CSST - WHMIS 1988	Class D2B - Toxic material causing other toxic effects	+1
	U	LT-UNK	EC - CEPA DSL	Inherently Toxic to Humans (iTH)	

Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	H	LT-UNK	GHS - Japan	H371 - May cause damage to organs [Specific target organs/systemic toxicity following single exposure - Category 2]

Restricted Substance Lists (4)

- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- GSPI - Six Classes of Problematic Chemicals: Some Solvents
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

Positive Lists (1)

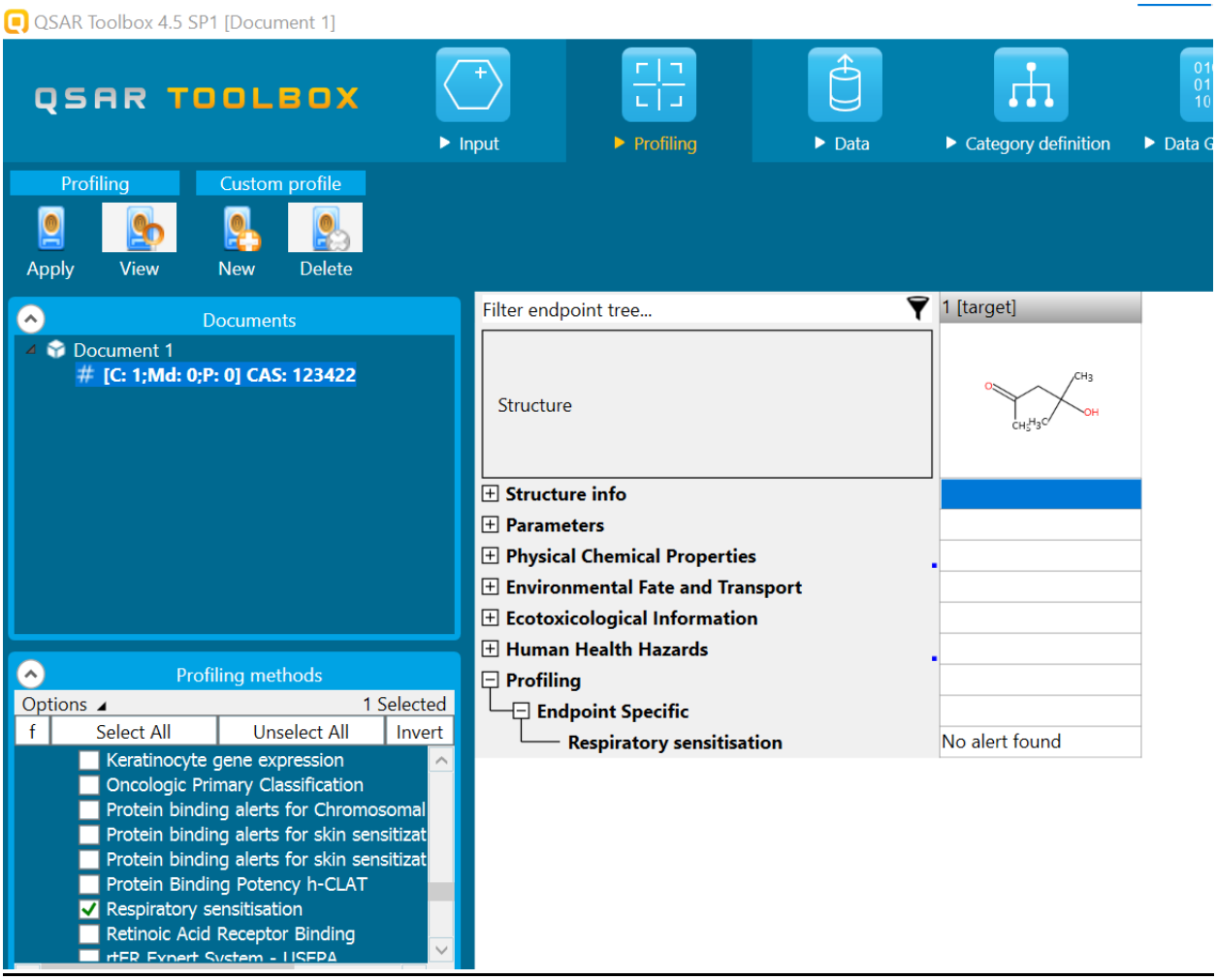
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients

Discussions

No discussions have been posted yet.

Ask a question about this chemical in the forums >

APPENDIX D: OECD Toolbox Respiratory Sensitization Results for Diacetone Alcohol (CAS #123-42-2)



APPENDIX E: EPI Suite™ Modeling Results for Diacetone Alcohol (CAS #123-42-2)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 000123-42-2
SMILES : O=C(CC(O)(C)C)C
CHEM : 4-HYDROXY-4-METHYL-2-PENTANONE
MOL FOR: C6 H12 O2
MOL WT : 116.16
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): -0.14
Boiling Point (deg C) : 167.90
Melting Point (deg C) : -44.00
Vapor Pressure (mm Hg) : 1.71
Water Solubility (mg/L): 1E+006
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = -0.34
Log Kow (Exper. database match) = -0.14
Exper. Ref: SAKURATANI,Y ET AL. (2007)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 162.64 (Adapted Stein & Brown method)
Melting Pt (deg C): -10.65 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.489 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 65.2 (Mean VP of Antoine & Grain methods)
MP (exp database): -44 deg C
BP (exp database): 167.9 deg C
VP (exp database): 1.71E+00 mm Hg (2.28E+002 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 8.948e+005
log Kow used: -0.14 (user entered)
melt pt used: -44.00 deg C
Water Sol (Exper. database match) = 1e+006 mg/L (25 deg C)
Exper. Ref: LANDE,SS ET AL. (1976)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 7.8344e+005 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Ketone alcohols

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 4.24E-009 atm-m3/mole (4.30E-004 Pa-m3/mole)
Group Method: 1.38E-009 atm-m3/mole (1.39E-004 Pa-m3/mole)

Exper Database: 2.61E-07 atm-m3/mole (2.64E-002 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.614E-007 atm-m3/mole (2.648E-002 Pa-m3/mole)
VP: 1.71 mm Hg (source: User-Entered)
WS: 1E+006 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -0.14 (user entered)
Log Kaw used: -4.972 (exp database)
Log Koa (KOAWIN v1.10 estimate): 4.832
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.5151
Biowin2 (Non-Linear Model) : 0.3064
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.7079 (weeks-months)
Biowin4 (Primary Survey Model) : 3.5045 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4471
Biowin6 (MITI Non-Linear Model): 0.3670
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.1028
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 228 Pa (1.71 mm Hg)
Log Koa (Koawin est): 4.832
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.32E-008
Octanol/air (Koa) model: 1.67E-008
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 4.75E-007
Mackay model : 1.05E-006
Octanol/air (Koa) model: 1.33E-006

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 3.9375 E-12 cm3/molecule-sec
Half-Life = 2.716 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 32.597 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

7.64E-007 (Junge-Pankow, Mackay avg)
1.33E-006 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1 L/kg (MCI method)
Log Koc: 0.000 (MCI method)
Koc : 4.284 L/kg (Kow method)
Log Koc: 0.632 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.5970 days (HL = 0.0253 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.031 (BCF = 0.9318)
Log BAF Arnot-Gobas method (upper trophic) = -0.031 (BAF = 0.9318)
log Kow used: -0.14 (user entered)

Volatilization from Water:
Henry LC: 2.61E-007 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 2419 hours (100.8 days)
Half-Life from Model Lake : 2.648E+004 hours (1103 days)

Removal In Wastewater Treatment:
Total removal: 1.86 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 percent
Total to Air: 0.01 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**1.72**	**64.2**	**1000**
Water	**49.3**	**900**	**1000**
Soil	**48.9**	**1.8e+003**	**1000**
Sediment	**0.097**	**8.1e+003**	**0**

Persistence Time: 705 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.72	64.2	1000
Water	49.3	900	1000
water	(49.3)		
biota	(1.79e-006)		
suspended sediment	(7.4e-005)		

Soil	48.9	1.8e+003	1000
Sediment	0.097	8.1e+003	0

Persistence Time: 705 hr

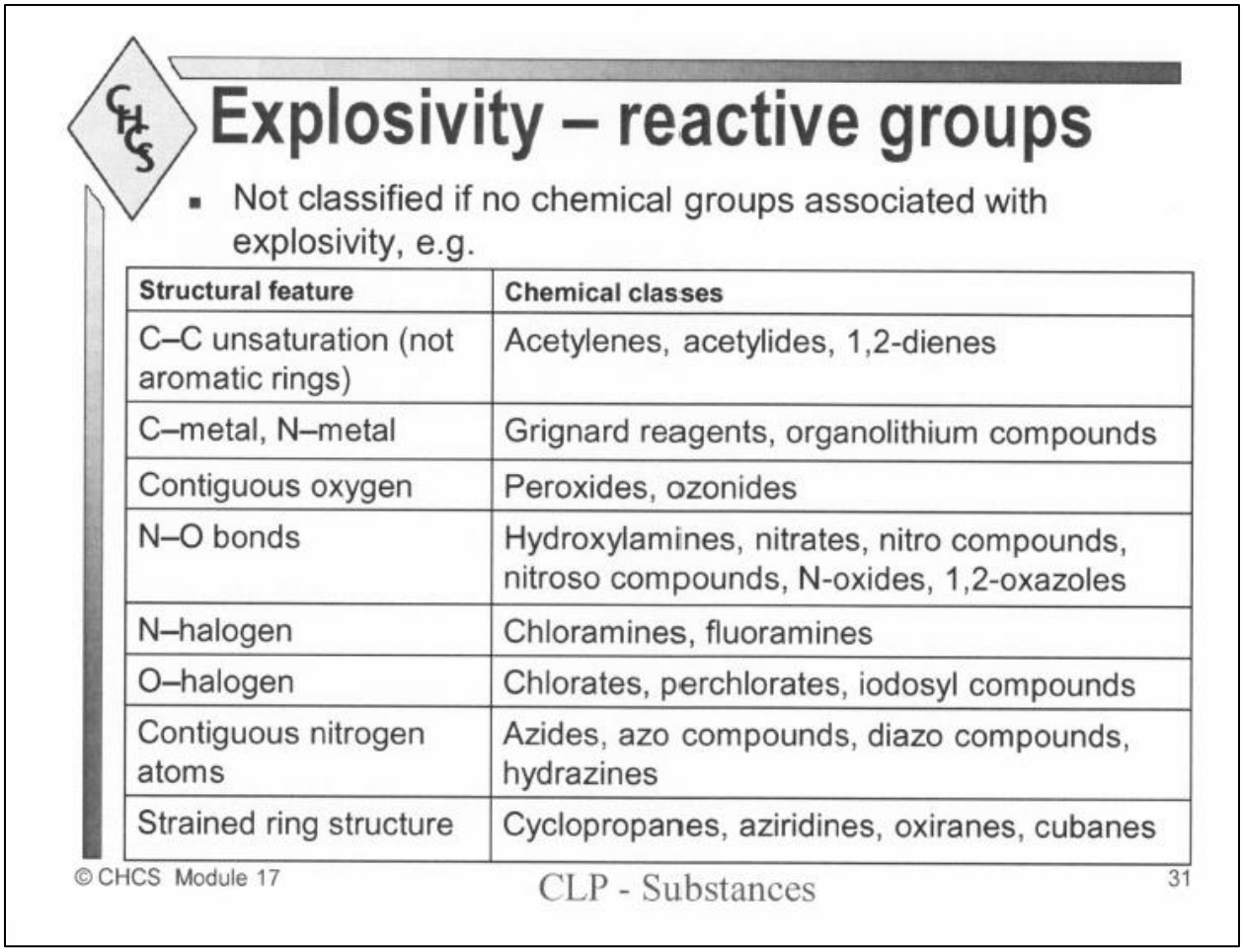
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.75	64.2	1000
Water	50.4	900	1000
water	(50.4)		
biota	(1.83e-006)		
suspended sediment	(2.25e-005)		
Soil	47.8	1.8e+003	1000
Sediment	0.0974	8.1e+003	0

Persistence Time: 695 hr

APPENDIX F: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

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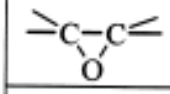
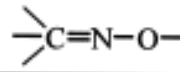
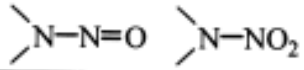
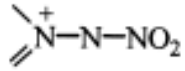
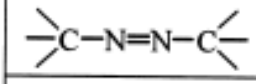
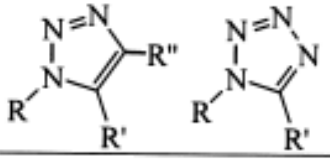
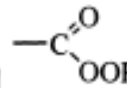
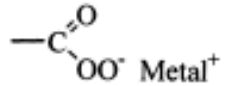
Explosivity – Full List

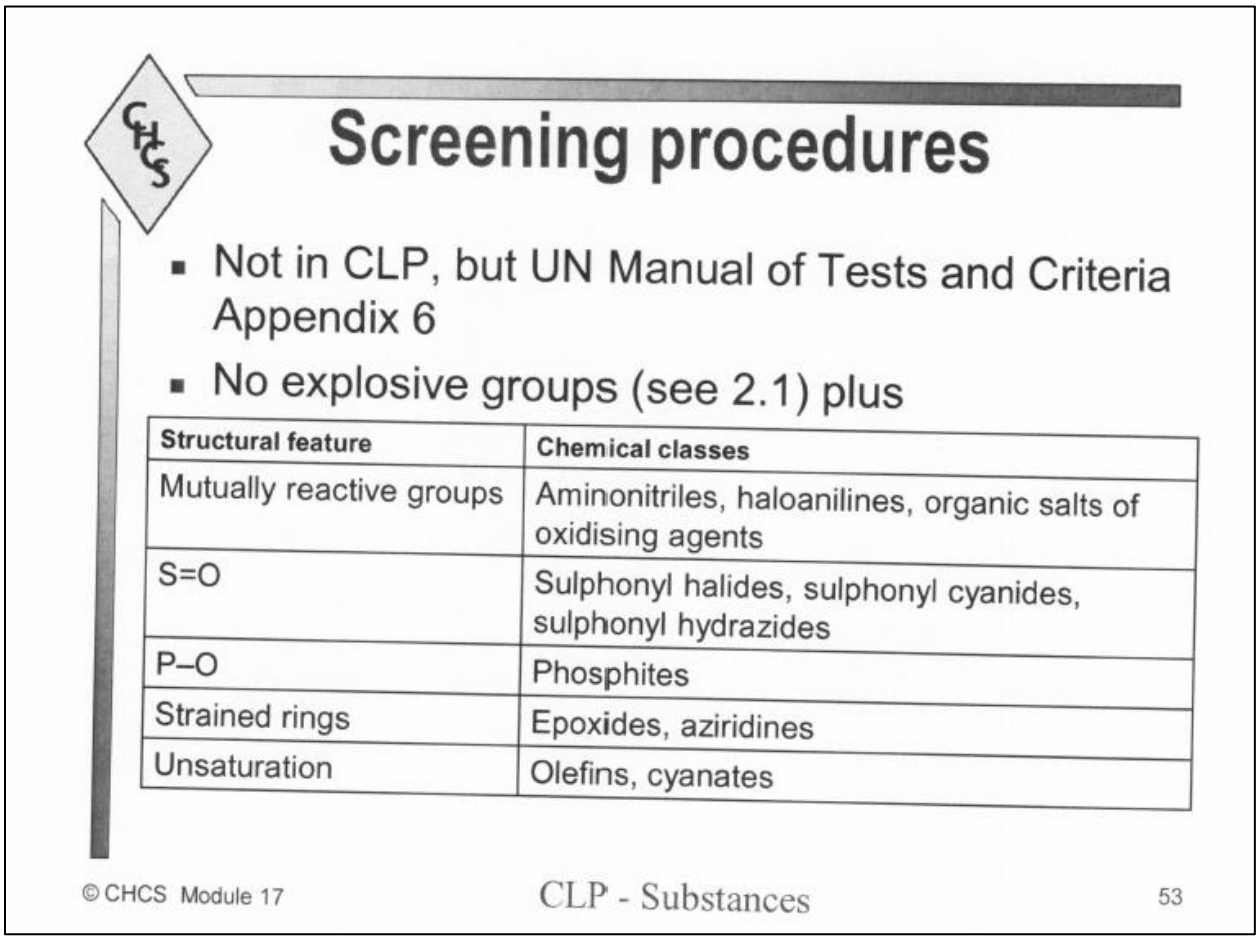
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



APPENDIX G: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for diacetone alcohol. The GreenScreen® Benchmark score for diacetone alcohol has not changed over time. The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria, and ToxServices assigned a Benchmark 2 (BM-2). The BM-2 score was maintained with version 1.4 updates in 2019 and with this most recent update in 2023.

Table 5: Change in GreenScreen® Benchmark™ for Diacetone Alcohol

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
September 19, 2014	BM-2	v.1.2	New assessment
June 28, 2019	BM-2	v.1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
January 25, 2023	BM-2	v.1.4	No change in BM score. The GreenScreen® assessment was updated with additional studies. Upon a weight of evidence evaluation, the following endpoints has revised hazard scores: reproductive toxicity (from *Moderate* (low confidence) to **Low** (high confidence)), developmental toxicity (change of confidence from low to high), single dose systemic toxicity (change of confidence from high to low), eye irritation (change of confidence from high to low). These changes do not affect the final benchmark score.

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