Regulatory Management Option Analysis Conclusion Document

Substance Name: Butanedione (Diacetyl)

EC Number: 207-069-8

CAS Number: 431-03-8

Authority: The Netherlands

Date: January 2023

Overview:

Diacetyl is commonly used as a flavouring substance. Currently, there are two registrations, for intermediate use only. It is self-classified by >1600 notifiers. In 2016, diacetyl was banned in e-liquids and e-cigarettes in the EU, due to the potential to induce severe bronchiolitis obliterans, a rare but potentially fatal disease. Since then, numerous cases of obliterative bronchiolitis have been observed in the microwave popcorn industry. As other exposure routes of this extensively used (flavouring) substance are envisioned, there is a need to further evaluate this potentially widespread exposure, and limit the inhalatory exposure of diacetyl.

Version 2.1
October 2015

DISCLAIMER

The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA or the Member States may initiate at a later stage. Risk Management Option Analyses and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

Foreword

The purpose of Risk Management Option analysis (RMOA) is to help authorities decide whether further regulatory risk management activities are required for a substance and to identify the most appropriate instrument to address a concern.

RMOA is a voluntary step, i.e., it is not part of the processes as defined in the legislation. For authorities, documenting the RMOA allows the sharing of information and promoting early discussion, which helps lead to a common understanding on the action pursued. A Member State or ECHA (at the request of the Commission) can carry out this case-by-case analysis in order to conclude whether a substance is a 'relevant substance of very high concern (SVHC)' in the sense of the SVHC Roadmap to 2020[1].

An RMOA can conclude that regulatory risk management at EU level is required for a substance (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. Any subsequent regulatory processes under the REACH Regulation include consultation of interested parties and appropriate decision making involving Member State Competent Authorities and the European Commission as defined in REACH.

This Conclusion document provides the outcome of the RMOA carried out by the author authority. In this conclusion document, the authority considers how the available information collected on the substance can be used to conclude whether regulatory risk management activities are required for a substance and which is the most appropriate instrument to address a concern. With this Conclusion document the Commission, the competent authorities of the other Member States and stakeholders are informed of the considerations of the author authority. In case the author authority proposes in this conclusion document further regulatory risk management measures, this shall not be considered initiating those other measures or processes. Since this document only reflects the views of the author authority, it does not preclude Member States or the European Commission from considering or initiating regulatory risk management measures which they deem appropriate.

[1] For more information on the SVHC Roadmap: http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/svhc-roadmap-to-2020-implementation

1. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Similar substances/ Grouping possibilities

It is concluded that 2,3-pentanedione has a similar toxicity to 2,3-butanedione (diacetyl). For the scope of this RMOA no grouping has been applied. However, since substitution of diacetyl with 2,3-pentanedione is already observed, it is recommended to also include this substance in regulatory measures to overcome regrettable substitution. In addition, no grouping approach (ARN) has been published by ECHA for this specific substance yet. In a confidential Annex of the final version of the RMOA more information about grouping possibilities is included.

Relevant Legislation

Diacetyl is preregistered and is self-classified by in total 1674 notifiers. There are currently two registrations. However, those are for intermediate use only (November 2022).

The European Commission has declared diacetyl is legal for use as a flavouring substance in all EU states. EFSA (European Food Safety Authority) is the relevant authority given this use application. According to Regulation (EC) No 1334/2008, the use of diacetyl as flavouring substance (FL No. 07.052) is authorised without any restrictions. This authorisation is based on an evaluation of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The Committee concluded that the use of diacetyl as flavouring substance does not pose a safety concern at the estimated level of intake (JECFA 1998)[2].

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of 11 compounds belonging to chemical group 10 (secondary aliphatic saturated or unsaturated alcohols, ketones, ketals and esters with a second secondary or tertiary oxygenated functional group). They are currently authorised as flavours in food. The FEEDAP Panel concluded that diacetyl [07.052] is safe at the proposed maximum use level of 25 mg/kg complete feed for all target species, except piglets, chickens for fattening, laying hens and cats, for which the proposed normal use level of 5 mg/kg is safe. For diacetyl, the maximum proposed use levels are considered safe for the environment[3].

The EC Scientific Committee on Occupational Exposure Limits (SCOEL) recommendation on diacetyl (adopted June 2014):

8-hour TWA:	0.02 ppm (0.07 mg/m^3)
STEL:	0.10 ppm (0.36 mg/m^3)
BLV:	Not assigned
Additional categorisation:	-
Notation:	-

These proposed occupational exposure limits (OELs) for diacetyl were based on various interpretations of an assumed causal association between diacetyl exposure and respiratory obstruction at the “sentinel plant,” as originally reported in Kreiss et al.

[2] JECFA (1998) Joint FAO/WHO Expert Committee on Food Additives. Safety evaluation of aliphatic acyclic and alicyclic *alpha*-diketones and related *alpha*-hydroxyketones. Prepared by the fifty-first meeting of the Joint FAO/WHO Expert Committtee on Food Additives. WHO Food Additives Series 42, 353-379. https://inchem.org/documents/jecfa/jecmono/v042je20.htm

[3] http://europa.eu/rapid/press-release_IP-16-1762_en.htm

(2002)[4]. In 2017 these indicative OELs have been established which obliges member states to set their own occupational exposure limit value.

In 2016, diacetyl was banned in e-liquids and e-cigarettes in the EU under the EU Tobacco Products Directive[5] due to the potential to induce severe bronchiolitis obliterans (Allen, Flanigan et al. 2016)[6].

Diacetyl is not listed in Annex VI of the CLP, has 28 aggregated C&L nofifications of in total 1674 notifiers in the C&L Inventory (November 2022). The following hazard classes are listed in the aggregated self classifications: Acute Tox. 3 (H331, inhalation), Acute Tox. 3 (H301, oral), Eye Dam. 1 (H318), Skin Sens 1A (H317), possibly Mut. 2 (H341), possibly Carc. 2 (H351), and STOT RE 1 (H372, inhalation/nasal and lung).

2. CONCLUSION OF RMOA

Diacetyl is used as a flavouring agent for which specific legislation is applicable and for which EFSA is the responsible legal entity. However, the risks arising from inhalatory exposure to diacetyl, arinsing from the use of this substance as an intermediate at the working place seem not to be covered sufficiently by the food flavourings Regulation (EC) No 1334/2008.

The following risk management measures are concluded appropriate to address the concern for adverse effects of diacetyl. It is proposed to:

- Draft a proposal for harmonised classification and labelling for diacetyl as Acute Tox. 3 (H331, inhalation), Acute Tox. 3 (H301, oral), Eye Dam. 1 (H318), Skin Sens 1A (H317), possibly Mut. 2 (H341), possibly Carc. 2 (H351), and STOT RE 1 (H372, inhalation/nasal and lung).
- Consider also draft proposals for harmonized classification of other structurally-related substances (alpha-diketones) such as 2,3-pentanedione (CAS no. 600-14-6) with similar reactivity and toxicity profile.
- Monitor whether the current OEL of 0.02 ppm [SCOEL 2014] is sufficiently protective by monitoring for decreasing incidence of obliterative bronchiolitis for workers in relevant fields of work (NIOSH recommends an REL of 5 ppb for diacetyl as a time-weighted average (TWA) for up to 8 hours/day during a 40-hour workweek [NIOSH, 2016]).
- Multiple flavouring agents are causing the same effects, grouping approach would be more effective than addressing diacetyl as an individual substance. In case of additional regulatory management measures 2,3-pentanedione should be included next to diacetyl to avoid regrettable substitution. For the other comparable flavouring agents also OELs should be derived before the addtionrule can be applied.

3. NEED FOR FOLLOW-UP REGULATORY ACTION AT EU LEVEL

SVHC Roadmap 2020 criteria:

	Yes	No
a) Art 57 criteria fulfilled?	X	

[4] Kreiss, K., A. Gomaa, G. Kullman, K. Fedan, E. J. Simoes and P. L. Enright (2002). "Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant." N Engl J Med 347(5): 330-338.

[5] http://europa.eu/rapid/press-release_IP-16-1762_en.htm

[6] Allen, J. G., S. S. Flanigan, M. LeBlanc, J. Vallarino, P. MacNaughton, J. H. Stewart and D. C. Christiani (2016). "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes." Environ Health Perspect 124(6): 733-739.

	Possibly ELoC based on the effects on Resp. Sys.	
b) Registrations in accordance with Article 10?		X
c) Registrations include uses within scope of authorisation?		X
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?		X

Diacetyl is one of the main components in butter flavoring that imparts a buttery taste, and it has been identified as a prominent volatile organic compound (VOC) in air samples from microwave popcorn plants and flavoring manufacturing plants. Diacetyl is used as a natural and artificial flavoring ingredient and aroma carrier in bakery products, dairy products, snack foods, and more. It is mainly used as a butter flavoring but is also used in the flavor formulation of a number of other flavors, including but not limited to strawberry, caramel, hazelnut, and butterscotch. It is also present as a natural byproduct in some fermented food products such as beer and roasted food products such as coffee. Due to the severe irreversible lung disease obliterative bronchiolitis associated with occupational (and incidentally consumer) exposures, diacytel may meet the Art. 57 criteria for equivalent level of concern (57f). There is a concern for the association of diacetyl with respiratory disease for both occupational and to a lesser extend for consumer exposure. During manufacture or use, the substance may pose risks, primarily via inhalation of vapour, dust and particulates.

3.1 Harmonised classification and labelling

For diacetyl no harmonised classification and labelling has been established and it is therefore not listed in Annex VI. The available data furthermore suggest that the substance could be harmonized under CLP as Acute Tox. 3 (H331), Eye Dam. 1 (H318), Skin Sens 1A (H317), possibly Mut. 2 (H341), possibly Carc. 2 (H351), and STOT RE 1 (H372, inhalation/nasal and lung) classification.

Harmonized classification will ensure that the hazards presented by the substance are clearly communicated to workers, consumers and the public at large (although food and flavorings are excluded) and instigates the implementation of proper risk management measures at the workplace and public areas. It is therefore concluded that CLH for Acute Tox. 3 (H331, inhalation), Acute Tox. 3 (H301, oral), Eye Dam. 1 (H318), Skin Sens 1A (H317), possibly Mut. 2 (H341), possibly Carc. 2 (H351), and STOT RE 1 (H372, inhalation/nasal and lung) is an appropriate risk management option for diacetyl.

3.2 Substance evaluation

The information available suggests that there are enough animal and epidemiological data showing the association of exposure to diacetyl with the severe irreversible lung disease obliterative bronchiolitis. The substance is registered twice, but for intermediate uses only. It is therefore suggested to start with the CLH process. For the moment it can be concluded that there is no need to evaluate the substance in more detail.

3.3 Identification as a substance of very high concern, SVHC (first step towards authorisation)

Identifying diacetyl as an SVHC may address the concern for this substance with the eventual purpose of Authorization as a possible risk management option to regulate the current concern for workers and consumers.

Based on the available information, diacetyl may be identified as an SVHC based on

article 57(f) because of its severe irreversible lung disease obliterative bronchiolitis as Equivalent Level of Concern. As the table (SVHC criteria with respect to the SVHC 2020 Roadmap) points out, only one out of four criteria is met. Therefore it can be concluded that SVHC identification seems not an effective risk management option in regulating the risks related tot the use of diacetyl.

In addition, in Title I of REACH, Article 2 (5) it is mentioned that Titles II, V, VI and VII are not applicable for food, food additives and flavorings in food. Title VII addresses Authorisation. Therefore authorisation is not an option.

3.4 Restriction under REACH

Restriction applies if there is an unacceptable risk to human health or the environment arising from the manufacture, use or placing on the market of substances. Diacetyl is of concern to occupucational health and to a lesser extent to consumer exposure. A total ban on the manufacture and use of the substance would prevent all (potential) health risks. However, a total ban may be neither necessary nor proportionate. Restriction of specific uses can be considered, but seems not a suitable risk management option based on:

- There are no full registrations (diacetyl is only registered as an intermediate) and therefore no or limited REACH relevant use;
- Exposure levels for workers are already decreasing over the last years based on (voluntary) measures from industry;
- Numerous reference values are already set (OEL's).

3.5 Other Union-wide regulatory measures

Processes where diacetyl is manufactured, handled, or used include blending, mixing, and handling of flavoring compounds in liquid and powder form are similar to those of other industries and may allow for common approaches to reduce employee exposure. Traditionally, a hierarchy of controls has been used as a means of determining how to implement feasible and effective controls, which typically include according to declining order: elimination, substitution, engineering controls, administrative controls and personal protective equipment (PPE). The design concepts required for working with hazardous materials include specification of general ventilation, local exhaust ventilation, maintenance, cleaning and disposal, personal protective equipment, exposure monitoring, and medical surveillance. Bag emptying, bag filling, charging tanks, benchtop weighing and handling, and drum filling and emptying are a few of the production processes of concern. Special attention should be given to manual handling of flavoring compounds, particularly in heated processes, and when spraying flavoring compounds. An overview of best practices to reduce diacetyl and 2,3 pentanedione exposure is published by NIOSH (2015).[7] Research on food industry practices has led to the development of engineering controls that may help reduce employee exposure to diacetyl. A 3-year study of a microwave popcorn production facility showed that the use of exposure controls can dramatically reduce diacetyl concentrations in mixing rooms and for all production employees [Kanwal et al. 2011][8]. As a result of the implementation of exposure controls, average combined personal and area diacetyl air concentrations declined an order of magnitude in the mixing room (from 57.2 ppm to 2.88 ppm) while concentrations in the quality control laboratory (from 0.82 ppm to < LOD) and packaging area (from 2.76 ppm

[7] NIOSH (2015). "Best practices; engineering controls, work practices, and expsure monitoring for occupational exposures to diatyl and 2,3-pentanedione. By Dunn KH, McKernan LT, Garcia A. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication 2015-197.

[8] Kanwal, R., G. Kullman, K. B. Fedan and K. Kreiss (2011). "Occupational lung disease risk and exposure to butter-flavoring chemicals after implementation of controls at a microwave popcorn plant." Public Health Rep 126(4): 480-494.

to < LOD for machine operators) declined to below detectable limits. These interventions included providing general room exhaust ventilation to the mixing room and local exhaust ventilation for the heated flavoring and mixing tanks. Closed transfer processes were implemented through the installation of a pump to transfer heated butter flavorings from the holding tanks to oil/flavor mixing tanks. The building of an enclosure for all oil/flavor holding tanks and installing local exhaust ventilation on all tanks further reduced exposures to employees in the packaging area of this plant.

Although engineering controls can be effective for some processes, tasks associated with transfer of diacetyl may continue to pose risk to the employees even following the implementation of controls. For example, mixers may continue to be exposed at levels above the the recommended exposure limit (REL) of 5 ppb [NIOSH, 2016] for diacetyl when handling butter flavorings and from tank emissions. However, these exposures can be reduced through the implementation of closed transfer systems and local exhaust ventilation approaches. The frequent use of personal protective equipment may be required for some employees who handle diacetyl, diacetyl-containing flavorings or flavored products. The frequent use of personal protective equipment, including respirators, (PPE) may be required during job tasks for which (1) airborne concentrations of diacetyl (e.g., pouring, mixing, packaging) above the REL exist, (2) the airborne concentration of diacetyl is unknown or unpredictable, and (3) job tasks are associated with highly variable airborne concentrations because of workplace conditions or the manner in which the job is performed. In all work environments where diacetyl, diacetyl-containing flavorings or flavored products are found, control of exposure through engineering controls should be the highest priority. Besides, the Flavoring and Extract Manufacturers Association (FEMA) of the United States recommends the warning statement for the products containing diacetyl [NIOSH, 2016][9].

NIOSH recommends a REL of 5 ppb for diacetyl as a time-weighted average (TWA) for up to 8 hours/day during a 40-hour workweek [NIOSH, 2016]. NIOSH has determined that employees exposed to diacetyl at this level for 8 hours a day, 40 hours a week for a 45-year working lifetime should have no more than an 1/1,000 excess risk of lung function falling below the lower limit of normal due to diacetyl exposure. To ensure that employee exposures are routinely below the REL for diacetyl, NIOSH also recommends using an action level (AL) of 2.6 ppb with the exposure monitoring program to ensure that all control efforts (engineering controls, medical surveillance, and work practices) are in place and working properly. When exposures exceed the AL, employers should take corrective action (determine the source of exposure, identify methods for controlling exposure) to ensure that exposures are maintained below the REL. NIOSH is also recommending a short-term exposure limit (STEL) for diacetyl of 25 ppb for a 15-minute time period. The establishment of a STEL is based on the concern that peak exposures may have greater toxicity than the same total dose spread out over a longer period of time. A TLV-TWA of 0.01 ppm (0.04 mg/m3) and a TLV-STEL of 0.02 ppm (0.07 mg/m3) have been proposed by the ACGIH for occupational exposure to diacetyl (ACGIH 2012).

For substances for which exposure in the workplace is expected, risks can be controlled by setting an European Occupational Exposure Limit (OEL). In December 2014, the Scientific Committee on Occupational Exposure Limits (SCOEL) published a report that considered diacetyl as being able to cause subclinical to severe fixed airway obstruction, which is the critical health effect for recommending an OEL of 0.02 ppm (mg/m^3, 8-hour TWA). This SCOEL recommended also a STEL of 0.1 ppm (0.36 mg/m^3). Althought these OELs were set some years ago, it is yet unclear whether these OELs are met at the working place, if they are sufficiently protective and if there are still cases reported of bronchiolitis obliterans.

[9] NIOSH (2016). "National Institute of Occupational Safety and Health (NIOSH): Criteria for a recommended standard. Occupational exposure to diacetyl and 2,3-pentanedione. External review draft, August 12, 2011.": https://www.cdc.gov/niosh/docs/2016-111/.

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

Follow-up action	Date for follow-up	Actor
CLH dossier for diacetyl and 2,3-pentanedione (and other alpha-diketones)		
OEL monitoring		Member states (since an iOEL forms the basis)
OEL-derivation for other comparable flavorings		