# Annex XV dossier

# PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1A OR 1B, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

**Substance Name(s):** Lead di(acetate)

**EC Number(s):** 206-104-4

**CAS Number(s):** 301-04-2

**Submitted by:** The Netherlands

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# TABLES

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**Substance Name(s):** Lead di(acetate)

**EC Number(s):** 206-104-4

**CAS number(s):** 301-04-2

The substance is proposed to be identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 1A.

Some lead salts are already placed on the candidate list of substances of very high concern, on basis of their reprotoxic effects. Inclusion of lead di(acetate) on the candidate list would prevent the risk that lead di(acetate) will be used as an alternative for the lead salts which are already on the SVHC list.

**Summary of how the substance meets the criteria set out in Article 57 (c) of REACH (Toxic to Reproduction 1A).**

Lead di(acetate) (EC number: 206-104-4; CAS number: 301-04-2) is covered by index number 082-005-00-8 of Regulation (EC) No 1272/2008[1] in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances), as toxic to reproduction, Repr. 1A (H360D: May damage the unborn child).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

**Registration dossiers submitted for the substance:**

Yes

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

# PART I

# JUSTIFICATION

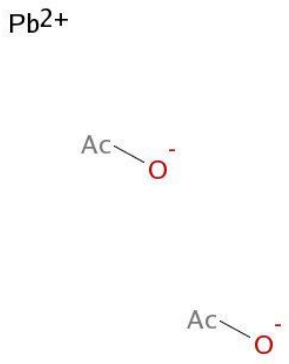
# 1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

## 1.1 Name and other identifiers of the substance

Table 1: Substance identity

| | |
|---|---|
| **EC number:** | 206-104-4 |
| **EC name:** | Lead di(acetate) |
| **CAS number (in the EC inventory):** | 301-04-2 |
| **CAS number:** | 301-04-2 |
| **CAS name:** | Acetic acid, lead(2+) salt (2:1) |
| **IUPAC name:** | Lead(2+) diacetate |
| **Index number in Annex VI of the CLP Regulation** | 082-005-00-8 |
| **Molecular formula:** | $C_4H_6O_4Pb$ |
| **Molecular weight range:** | 325.2869 g/mol |
| **Synonyms:** | *Acetic acid, lead(2++) salt*<br>*Acetic acid, lead(2+) salt*<br>*Lead acetate*<br>*Plomo(II) Acetato 3-hidrato*<br>*Lead(2+) diacetate*<br>*Lead(II) diethanoate-3-water* |

**Structural formula:**



### 1.2 Composition of the substance

**Name:** Lead di(acetate)

**Description**: mixed organic – inorganic salt.

**Degree of purity:** ≥ 80% (w/w).

Table 2: Constituents

| **Constituents** | **Typical concentration** | **Concentration range** | **Remarks** |
|---|---|---|---|
| lead di(acetate)<br>EC no: 206-104-4 | | ≥ 80 % (w/w) | |

### 1.3 Physico-chemical properties

Table 3: Overview of physicochemical properties[1]

| Property | Value | Remarks |
|---|---|---|
| Physical state at 20°C and 101.3 kPa | *A white to colourless crystalline solid* | *IUCLID* |
| Melting/freezing point | *204 ºC* | *IUCLID: from Gmelin Handbook of inorganic chemistry Pb Tl. C Lfg.2 Part C p. 741* |
| Boiling point | *Decomposition range > 204- 236 °C* | *Boiling point not applicable as substance is a solid.*<br>*Gmelin Handbook of inorganic chemistry Pb Tl. C Lfg.2 Part C p.742.* |
| Vapour pressure | | ***Study scientifically not justified:***<br>*Lead di(acetate) is an inorganic metal salt, which contains lead cations and acetate anions in a crystalline matrix. The melting point of lead acetate is 204°C, followed by decomposition under atmospheric conditions. Thus, under typical atmospheric conditions, lead di(acetate) exists in the solid phase and not in the gaseous phase. Therefore, the vapour pressure, i.e. the saturation pressure above a solid or liquid, is not relevant for any hazard assessment of this substance. However, if lead di(acetate) gets in contact with water, acetic acid forms in parts, which has a vapour pressure of 20.9 hPa at 25°C (experimental database provided by EpiSuite v4.0).*<br>*In consequence, testing need* |

[1] The references of the values reported in Table 3 are available in the technical dossier.

| | | |
|---|---|---|
| | | *for vapour pressure is waived for this substance, since such testing would not provide any meaningful information on the substance itself, whereas the vapour pressure of acetic acid is provided above. Ref: letter from the joint submission registrant to NL-CA.* |
| Water solubility | *44.3 g/100 mL at 20 ºC.* | *IUCLID: CRC Handbook of Chemistry and Physics 65th Edition B-105* |
| Partition coefficient n-octanol/water (log value) | - | *Waived, in view of the inorganic nature of the substance.* |
| Dissociation constant | - | *Waived, in view of the inorganic nature of the substance.* |

## 2 HARMONISED CLASSIFICATION AND LABELLING

Lead di(acetate) is listed as Index number 082-005-00-8 in Regulation (EC) no 1272/2008 and classified in 3.1 as follows:

Table 4 : Harmonised classification according to Annex VI, Part 3, Table 3.1 of Regulation (EC) No 1272/2008

| **Index No** | **Classification** | | **Labelling** | | |
|---|---|---|---|---|---|
| | **Hazard Class and Category Code#** | **Hazard statement Code# #** | **Pictogram, Signal Word Code** | **Hazard statement Code# #** | **Notes** |
| 082-005-00-8 | Repr. 1A<br>STOT RE 2 *<br>Aquatic Acute 1<br>Aquatic Chronic 1 | H360Df<br>H373 **<br>H400<br>H410 | GHS08<br><br>GHS09<br>Dgr | H360Df<br>H373 **<br><br>H410 | Note 1 |

*: The classification shall be considered as a minimum classification. See, CLP regulation Annex VI paragraph 1.2.1.

**: The classification under 67/548 EEC indicating the route of exposure has been translated into the corresponding class and category according to this Regulation, but with a general hazard statement not specifying the route of exposure as the necessary information is not available. See, CLP regulation Annex VI paragraph 1.2.2.

# Hazard Class and Category Code:

| | |
|---|---|
| Repr. 1A | Toxic to Reproduction Category 1A |
| STOT RE 2 | Specific Target Organ Toxicity Repeated Exposure Category 2 |
| Aquatic Acute 1 | Acute Aquatic Toxicity Category 1 |
| Aquatic Chronic 1 | Chronic Aquatic Toxicity Category 1 |

# # Hazard statement Code:

| | |
|---|---|
| H360Df: | May damage the unborn child. Suspected of damaging fertility. |
| H373: | May cause damage to organs through prolonged or repeated exposure. |
| H400: | Very toxic to aquatic life |
| H410: | Very toxic to aquatic life with long lasting effects |

Note 1: The concentration stated or, in the absence of such concentrations, the generic concentrations of this Regulation (Table 3.1) or the generic concentrations of Directive 1999/45/EC (Table 3.2), are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture.

## 3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this type of dossier.

# 4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on harmonised classification and labelling.

# 5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this type of dossier.

# 6 CONCLUSIONS ON THE SVHC PROPERTIES

## 6.1 CMR assessment

Lead di(acetate) (EC number: 206-104-4; CAS number: 301-04-2) is covered by index number 082-005-00-8 of Regulation (EC) No 1272/2008[2] in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances), as toxic to reproduction, Repr. 1A (H360D: 'May damage the unborn child.). Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

# PART II

# INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

## INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES –CONCLUSIONS ON EXPOSURE

Tonnage:
According to the registration dossier (joint registration 1 – 10 tpa).

The following PROCs (process categories) are given within the lead di(acetate) registration dossier for manufacture of the substance:
PROC 1: Use in closed process, no likelihood of exposure.
PROC 3: Use in closed batch process (synthesis or formulation).
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises.
PROC 8b: Transfer of substance or preparation (charging / discharging) from / to vessels / large containers at dedicated facilities.
PROC 9: transfer of substance or preparation into small containers (dedicated filling line, including weighing) and formulated in preparations or in materials.

Industrial use:
Lead di(acetate) is reported to be used in the following product categories:
PC 9a: Coatings and paints, thinners, paint removes.
PC 9b: Fillers, putties, plasters, modelling clay.
PC 19: Intermediate.
PC 21: Laboratory chemicals.

At industrial sites lead di(acetate) is used for:
PROC 1: Use in closed process, no likelihood of exposure.
PROC 2: Use in closed, continuous process with occasional controlled exposure.
PROC 3: Use in closed batch process (synthesis or formulation).
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises.
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and / or significant contact.
PROC 8a: Transfer of substance or preparation (charging / discharging) from / to vessels / large containers at non-dedicated facilities.
PROC 8b: Transfer of substance or preparation (charging / discharging) from / to vessels / large containers at dedicated facilities.
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing).
PROC 10: Roller application or brushing,
PROC 13: treatment of articles by dipping and pouring,
PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation
PROC 15: Use as laboratory reagent

PROC 22: Potentially closed processing operations with minerals/metals at elevated temperature.

The reported sectors of use are:
SU 9: Manufacture of fine chemicals
SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)
SU 16: Manufacture of computer, electronic and optical products, electrical equipment

The environmental release categories mentioned in registrations are:
ERC 1: Manufacture of substance.
ERC 2; Formulation of preparation.
ERC 3: Formulation in materials.
ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles.
ERC 5: Industrial use resulting in inclusion into or onto a matrix.
ERC 6a: industrial use resulting in manufacture of another substance (use of intermediates).
ERC 6b: Industrial use of reactive processing aids.
ERC 7: Industrial use of substances in closed systems.

The reported use of lead di(acetate) as a hair dye is banned in the EU since 2010, according to the Cosmetics regulation 1223/2009, annex II, entry 289 (lead and lead compounds). It is based on article 15 of the regulation, which prohibits the use of substances with CMR 1A and 1B classification. The use as a hair dye is allowed in the USA with limitations, only for hair on the scalp and ≤ 0.6% lead (FD.gov site, accessed 23/02/2013).

Lead di(acetate)) is reported in the classification and labelling inventory (checked: 23-08-2013) with 279 notifications, divided into the following major classifications:

Repr. 2, STOT RE 2, aquatic acute 1 and aquatic chronic 1, number of notifiers: 93

Repr 1A, STOT RE 2, aquatic acute 1 and aquatic chronic 1 and note 1, number of notifiers: 80

Repr 1A, STOT RE 2, aquatic acute 1 and aquatic chronic 1, number of notifiers: 73

Repr 1A, STOT RE 2, aquatic acute 1 and note 1: 4

Not classified, number of notifiers: 29.

The amount of notifications can considered to be indicative for the use of the substance. The fact that there are 279 classification notifications indicates that lead di(acetate) is used by many users in small volumes (below 1 ton per year).

***CURRENT KNOWLEDGE ON ALTERNATIVES***

Metallic dryers accelerate the drying of paints, coatings and inks. Lead drier is mostly used for this type of paint catalyst. Other metallic dryers are: cobalt, manganese, calcium, zinc, zirconium, bismuth, lithium, iron, rare-earths and aluminium and barium. A new alternative for lead is bismuth used in combination with cobalt and manganese. Data on volumes is not available.

No specific data on alternatives and their production or uses as alternatives for lead di(acetate) are available.

***RISK RELATED INFORMATION***

Based on the properties of lead di(acetate) and the available information on uses, a potential risk to consumers cannot be excluded. However, no detailed risk assessment is available.
Lead di(acetate) is used in consumer products. Therefore, there is a potential risk for consumer exposure to lead di(acetate) from the use of the products containing lead di(acetate). Exposure can be dermal or via inhalation, oral exposure is expected to be minor.
An indicative risk assessment was derived to estimate the potential worst case consumer exposure using ECETOC-TRA and Consexpo programs. A DNEL /DMEL value is not available in the registration file or literature for lead di(acetate). Instead the oral No Significant Risk Level (NSLR) of 23 µg/day total intake from the California OEHHA database was used to compare with exposure estimates. It should be noted, that this NSLR value was based on carcinogenicity, not reproductive toxicity, which is the main endpoint for lead di(acetate). In addition, the models used are intended to be screening models. The indicative worst case values are:

- 37.0 mg/kg/day for textiles (dermal for clothing and towels), RCR 97,000. ECETOC-TRA assumes whole body exposure, which is likely to be an overestimate.
- $3.0 \times 10^{-3}$ mg/kg/day for painting (dermal and brush painting, RCR 7.9. Assumes a chronic internal dose.

The worst case risk characterisation for the use of textiles is very high, which is likely caused by the high default values used in the models. These default values were used because there is no or minimal information available on current uses in consumer products. For a further refinement of the risk assessment, proper information on the levels of exposure and amount of lead di(acetate) in textiles is needed.

**REFERENCES**

Analysis of the most appropriate risk management option for lead di(acetate), RMO report prepared by the Netherlands, November 2012.

Basketter, D. A. Lea, L. J. Cooper, K. J. Ryan, C. A. Gerberick, G. F. Dearman, R. J. Kimber, I. Identification of metal allergens in the local lymph node assay. American Journal of Contact Dermatitis 1999, 10, (4), 207-12. (IUCLID registration).

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California OEHHA Toxicity Criteria Database, http://www.oehha.ca.gov/tcdb/, accessed 19 June 2013.

Campbell, K. I.; George, E. L.; Hall, L. L.; Stara, J. F. Dermal irritancy of metal compounds. Studies with palladium, platinum, lead, and manganese compounds. Archives of Environmental Health 1975, 30, (4), 168-70. (IUCLID registration)

IUCLID registration (joint submission) of leaddi(acetate).

Kinkead E.D., Wolfe R.E, Single oral toxicity of various organic compounds. Journal of the American College of Toxicology; 1992; 11:713. (IUCLID registration)

Registration dossier of lead(IV) tetra acetate. ECHA, http://echa.europe.eu/web/guest/information-on-chemicals/registered-substances, accessed June 2013. Search item used was: 546-67-8.

Ronis, M.J.J. Gandy, J. and Badger, T. (1998b). Endocrine Mechanisms Underlying Reproductive Toxicity In The Developing Rat Chronically Exposed To Dietary Lead. J Toxicol Environ Health Part A 54:77-99.

Ronis, M.J.J., Badger, T.M., Shema, S.J., Roberson, P.K. and Fatima, S. (1998c). Effects On Pubertal Growth and Reproduction in Rats Exposed Continuously throughout Development. J Toxicol Environ Health Part A 53:327-341.

VRAR (2008). ILZRO and EBRC Consulting. Voluntary risk assessment report on lead and some inorganic lead compounds (VRAR); human health section. Final draft, d.d. 4 March 2008.

# ANNEX I. SUPPLEMENTARY INFORMATION ON HUMAN HEALTH EFFECTS

It is noted that only few studies performed with lead di(acetate) are reported in the IUCLID file. Additional studies performed with lead (IV) (tetra)acetate and other lead salts have been found. The studies described in this report originate from the IUCLID file for lead di(acetate) from the registrant and from the Voluntary risk assessment lead and lead compounds document (VRAR, 2008). The studies are most frequently performed with lead (tetra)acetate. The lead ion, in which no marked difference in toxicity is expected between the $Pb^{2+}$ and $Pb^{4+}$ ion, is considered to cause the effects discussed within this report.

Studies with experimental animals have utilised soluble lead compounds such as lead acetate or lead nitrate. Occupational and general population studies monitor exposure to mixed forms of lead, often of unknown speciation. However, on the assumption that the lead ion released by these compounds to varying extents will behave similarly to that released by soluble or mixed environmental exposures, an assessment can be made of the toxicokinetics and health effects potentially associated with these substances (VRAR, 2008). It should be noted that next to the test animal data adverse effects of lead on human health are frequently reported and well known, which are the most important basis for the classification Repr. 1A (Hazard statement: H360: May damage fertility or the unborn child; Specific effect: H360Df - May damage fertility. May damage the unborn child).

## I.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No data available on lead di(acetate).

## I.2 Acute toxicity

### I.2.1 Non-human information

#### I.2.1.1 Acute toxicity: oral

Lead acetate is not toxic to Spraque-Dawley rats following acute oral administration. Male and female rats were dosed via gavage at five dose levels in an OECD study (equivalent or similar to OECD Guideline 401). The oral LD50 for lead di(acetate) was found to be 4665 (3153 -6900) and 5610 mg/kg bw for male and female rats, respectively. It is reasonable to assume that the toxicity of lead salts is triggered by the lead cation and not the corresponding anion. The toxicity data from lead di(acetate) is therefore also used for other soluble lead salts.

#### I.2.1.2 Acute toxicity: inhalation

No data available on lead di(acetate).

#### I.2.1.3 Acute toxicity: dermal

No data available on lead di(acetate).

#### I.2.1.4 Acute toxicity: other routes

No data available on lead di(acetate).

### I.2.2 Human information

No data available on lead di(acetate).

## I.3 Irritation

### I.3.1 Skin irritation

No signs of skin irritation were observed in a study with albino rabbits (n=6) exposed to lead dichloride. Test performance is equivalent or similar to OECD 404. Irritation to skin was observed in none of the animals tested. Read-across approach is applied for lead di(acetate) based on the fact that the toxicity of lead salts is caused by the lead cation and not by the acetate anion. Furthermore, the toxicity of lead di(acetate) may reasonably be considered to be determined by the bioavailability of lead. As a first surrogate for bioavailability, the water solubility of a test substance may be used. Lead di(acetate) and lead dichloride are “soluble” to “very soluble” in water (443 g/L at 20°C and 10 g/L at 20°C/pH 4.2, respectively). Based on the result of lead dichloride it is assumed that lead di(acetate) is not irritating to skin.

### I.3.2 Eye irritation

Lead di(acetate) was tested in an *in-vitro* bovine corneal opacity and permeability study (BCOP) according to the OECD guideline (OECD 437; GLP) in 2010. A mean corrected in vitro irritation score (IVIS) of 76.6 was calculated and staining in two eyes out of the five tested eyes was observed. The two staining eyes had the highest score and it was not known if the staining influenced the score. The registrant considers lead acetate as a severe eye irritant under the conditions of this study.

## I.4 Corrosivity

No data available on lead di(acetate).

## I.5 Sensitisation

In a mouse local lymph node assay (LLNA, equivalent or similar to OECD 429) conducted with lead di(acetate) at three test levels of 2.5, 5 and 10%, SI indices of 0.7, 0.8, and 1.0 were calculated. No concentration dependent increase was observed. The stimulation index is > 3. Therefore, it was concluded that lead di(acetate) is not a skin sensitiser.

## I.6 Repeated dose toxicity

No data available on lead di(acetate).

## I.7 Mutagenicity

No data available on lead di(acetate).

## I.8 Carcinogenicity

No data available on lead di(acetate).

## I.9 Toxicity for reproduction

### I.9.1 Developmental toxicity

#### I.9.1.1 Non-human information

**General**.

A huge amount of data, mostly from literature, is available about effects on reproduction after exposure to lead ions. A voluntary risk assessment report on lead and some inorganic lead compound has been prepared by ILZRO and EBRC consulting group under contract to the LDAI lead risk assessment working group (VRAR, final draft march 2008). In this document, in the human health section, a summary is given of the effects of lead exposure. A few studies are described, which were also reported in the registration dossier of lead(IV) tetra acetate (ECHA site).

In a study (Ronis et al. 1998b) the effects of lifetime lead exposure on the development of the reproductive system and the underlying endocrine effects were examined. Rats were exposed to lead acetate in drinking water at 0.05%, 0.15% and 0.45% from gestational day 5. The exposure of the dams was continued until weaning and the offspring were exposed through the drinking water until sacrifice at age 21, 35, 55, and 85 days. A significant dose-response decrease in birth-weight and crown-to-rump length in all lead exposed litters was observed. Male secondary sex organ development and female vaginal opening were delayed with increasing lead dose, with statistically significant delays appearing to begin at 0.15% lead acetate.

In the second study (Ronis et al., 1998c) an assessment has been performed on the reproductive, endocrine, and growth effects of developmental lead exposure. Rats were exposed to 0.6% (502 mg/kg/day) lead acetate in drinking water ad libitum during different developmental periods. The study goal was to determine if lead effects were a result of continuous exposure to the lead ion of a secondary to disrupted neonatal "endocrine imprinting". Rats (Sprague Dawley) were exposed to lead according to the following schedules: 1) from gestation day 5 through birth; 2) during pregnancy and lactation; 3) during lactation only; 4) from birth through adulthood; or 5) from gestation day 5 through adulthood. Developmental aspects of the reproductive system, adult sex, steroid levels and growth rates in both males and females were determined. Birth weight in all animals exposed in utero was decreased and mean body weights were significantly decreased in all lead-treated groups up to weaning. Growth curves of all lead-treated groups were significantly reduced during lactation. In male pups exposed to lead during pregnancy and lactation, from birth through adulthood or from gestation day 5, growth rates were also significantly reduced during puberty. Post pubertal growth rates were unaffected in any lead-treated group. No evidence was found for an alteration of "endocrine imprinting" by lead. Exposure during pregnancy and lactation resulted in about 10% decreases in the body weight of pups post-puberty.

### I.9.2 Summary and discussion of reproductive toxicity.

Birth weight and crown-to-rump length has been affected significantly by lead acetate exposure through drinking water. Growth rates of all lead-exposed groups were significantly reduced during lactation.

## I.10 Other effects

No data available on lead di(acetate).