Committee for Risk Assessment (RAC)
Committee for Socio-economic Analysis (SEAC)

Opinion

on an Annex XV dossier proposing restrictions on

substances used in tattoo inks and permanent make-up

ECHA/RAC/RES-O-0000001412-86-240/F

ECHA/SEAC/ ECHA/SEAC/RES-O-0000001412-86-265/F

Compiled version prepared by the ECHA Secretariat of RAC's opinion (adopted 20 November 2018) and SEAC's opinion (adopted 15 March 2019)

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OPINION ON AN ANNEX XV DOSSIER - TATTOO INKS AND PERMANENT MAKE-UP

20 November 2018

ECHA/RAC/RES-O-0000001412-86-240/F

15 March 2019

ECHA/SEAC/ ECHA/SEAC/RES-O-0000001412-86-265/F

Opinion of the Committee for Risk Assessment

and

Opinion of the Committee for Socio-economic Analysis

on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular the definition of a restriction in Article 3(31) and Title VIII thereof, the Committee for Risk Assessment (RAC) has adopted an opinion in accordance with Article 70 of the REACH Regulation and the Committee for Socio-economic Analysis (SEAC) has adopted an opinion in accordance with Article 71 of the REACH Regulation on the proposal for restriction of

Chemical name:	**Substances used in tattoo inks and permanent make-up**
EC No.:	**-**
CAS No.:	**-**

This document presents the opinion adopted by RAC and the Committee's justification for its opinion. The Background Document, as a supportive document to both RAC and SEAC opinions and their justification, gives the details of the Dossier Submitters proposal amended for further information obtained during the public consultation and other relevant information resulting from the opinion making process.

PROCESS FOR ADOPTION OF THE OPINIONS

ECHA has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The Annex XV report conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at

https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/18114/term on **20/12/2017**. Interested parties were invited to submit comments and contributions by **20/06/2018**.

ADOPTION OF THE OPINION

ADOPTION OF THE OPINION OF RAC:

Rapporteur, appointed by RAC: Veda Varnai

Co-rapporteur, appointed by RAC: Boguslaw Baranski

The opinion of RAC as to whether the suggested restriction is appropriate in reducing the risk to human health and/or the environment was adopted in accordance with Article 70 of the REACH Regulation on **20 November 2018**.

The opinion takes into account the comments of interested parties provided in accordance with Article 69(6) of the REACH Regulation.

The opinion of RAC was adopted **by consensus**.

ADOPTION OF THE OPINION OF SEAC

Rapporteur, appointed by SEAC: Richard Luit

Co-rapporteur, appointed by SEAC: Jean-Marc Brignon

The draft opinion of SEAC

The draft opinion of SEAC on the proposed restriction and on its related socio-economic impact has been agreed in accordance with Article 71(1) of the REACH Regulation on **29 November 2018.**

The draft opinion takes into account the comments from the interested parties provided in accordance with Article 69(6)(a) of the REACH Regulation.

The draft opinion takes into account the socio-economic analysis, or information which can contribute to one, received from the interested parties provided in accordance with Article 69(6)(b) of the REACH Regulation.

The draft opinion was published at http://echa.europa.eu/restrictions-under-consideration/-/substance-rev/18114/term on **12 December 2018**. Interested parties were invited to submit comments on the draft opinion by **11 February 2019**.

The opinion of SEAC

The opinion of SEAC on the proposed restriction and on its related socio-economic impact was adopted in accordance with Article 71(1) and (2) of the REACH Regulation on ***15 March 2019***.

The opinion takes into account the comments of interested parties provided in accordance with Articles 69(6) and 71(1) of the REACH Regulation.

The opinion of SEAC was adopted ***by consensus*** of all members having the right to vote.

Contents

TABLES

A. OPINION OF RAC AND SEAC

The restriction options proposed by the Dossier Submitter are shown in Table 1 and Table 2:

Table 1. Restriction option 1 (RO1)

a) Substances in Part 3 of Annex VI to Regulation (EC) No 1272/2008 classified as: – carcinogenic, mutagenic, or toxic to reproduction category 1A, 1B, or 2 – skin sensitisers category 1, 1A or 1B – skin irritant or corrosive, category 1, 1A, 1B, 1C, or 2 – serious eye damage or eye irritant, category 1 or 2 b) Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009 c) Substances on Annex IV of Regulation (EC) 1223/2009 that are subject to conditions in columns g to i of that Annex d) Substances in Table A[3]	1. Tattoo inks shall not be placed on the market if they contain the substances specified below, unless a concentration limit is specified under paragraph 2. In the event a substance is subject to more than one of the conditions in paragraphs 1.a) to 1.c), the stricter condition applies: a. Tattoo inks shall not contain the following substances: i. Carcinogenic or mutagenic substances, category 1A, 1B or 2 excluding those substances classified only with the hazard statements H350 (inhalation) (May cause cancer by inhalation), H351 (inhalation) (Suspected of causing cancer by inhalation), H340 (inhalation) (May cause genetic defects via inhalation) and H341 (inhalation) (Suspected of causing genetic defects by inhalation) ii. Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009[1] iii. Substances in Annex IV of Regulation (EC) 1223/2009 with the following conditions in column g of that Annex: • Rinse-off products • Not to be used in products applied on mucous membranes • Not to be used in eye products b. Tattoo inks shall not be placed on the market if they contain the following substances in concentrations greater than 0.1% w/w: i. Skin sensitisers, category 1, 1A and 1B ii. Skin corrosive or irritant substances, category 1, 1A, 1B, 1C, and 2[2] iii. Serious eye damage/eye irritant , category 1 and 2[2] c. Tattoo inks shall not be placed on the market if they contain substances that are toxic to reproduction: i. Category 1A and 1B in concentrations greater than 0.0014 % w/w ii. Category 2 in concentrations greater than 0.014% w/w 2. Tattoo inks shall not be placed on the market if they contain substances listed in Table A,[3] exceeding the specified concentration limits, or Polycyclic-aromatic hydrocarbons (PAH), classified as carcinogenic or mutagenic categories 1A, 1B and 2 in individual concentrations exceeding 0.00005% w/w. 3. By way of derogation: a. paragraph 1.a.ii) and 1.a.iii) does not apply to substances

[1] This provision is recommended to apply one year after the substance is listed on Annex II

[2] The concentration limit applies to each individual substance

[3] Table A contains methanol, impurities listed in Table 3 of CoE ResAP(2008)1, PAAs, and azo dyes.

	(colourants) listed in Table B[4] or b. paragraph 1 does not apply to substances that are gases at standard temperature and pressure.[5] 4. Substances in Annex IV of Regulation (EC) 1223/2009 allowed in cosmetic products (except those in paragraph 1.a.iii) are also allowed in tattoo inks, subject to the conditions in columns h to i of that Annex, unless a lower concentration limit is specified in paragraphs 1 and 2. 5. Tattoo inks not meeting the requirements specified in paragraphs 1 to 4 shall not be used in tattoo procedures. 6. The person responsible for the placing on the market of a tattoo ink shall ensure that the label provides the following information: a. The intended use of the mixture as a tattoo ink; b. A reference number to uniquely identify the batch; c. The name of all substances used in the tattoo ink classified for human health in accordance with Annex I of Regulation 1272/2008 but not covered by the current restriction entry, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; d. The name of any additional substances covered by this restriction entry that are used in the tattoo ink, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; e. The phrase "Contains nickel. Can cause allergic reactions." if the tattoo ink contains nickel below the concentration limit specified in Table A. f. The phrase "Contains chromium (VI). Can cause allergic reactions." if the tattoo ink contains chromium (VI) below the concentration limit specified in Table A. g. Any relevant instructions for use, unless this duplicates a precautionary statement already required to be stated on the label by Regulation (EC) No 1272/2008. The labelling shall be clearly visible, easily legible and appropriately durable. The label shall be written in the official language(s) of the Member State(s) where the substance or mixture is placed on the market, unless the Member State(s) concerned provide(s) otherwise. Where necessary because of the size of the package, the labelling information shall be included in the instructions for use. The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure. 7. Definitions for the purpose of this restriction entry a. Tattoo ink is a mixture consisting of colorants and auxiliary ingredients administered by intentional intradermal injection whereby a permanent skin marking or design (a "tattoo" or

[4] Supplementary Table B (containing substances proposed for derogation of 1.a.ii) and 1.a.ii)) is included in Table 5 of the Background document

[5] I.e., substances which are gaseous at temperature of 20°C and standard pressure of 101.3 kPa, or generate a vapour pressure of more than 300 kPa at temperature of 50°C.

	"permanent make-up") is made. b. Tattoo procedure (also referred to as permanent make-up, micro-blading, cosmetic tattooing, micro-pigmentation) is any intentional introduction of tattoo ink into human skin. 8. The restriction shall apply one year after its entry into force.

Note: Supplementary Table A is included in Table 4 and Supplementary Table B in Table 5 of the Background document.

Table 2. Restriction option 2 (RO2)

a) Substances in Part 3 of Annex VI to Regulation (EC) No 1272/2008 classified as: - carcinogenic, mutagenic, or toxic to reproduction category 1A, 1B, or 2 - skin sensitisers, category 1, 1A or 1B - skin irritant or corrosive, category 1, 1A, 1B, 1C, or 2 - serious eye damage or eye irritant, category 1 or 2 b) Substances in Table A[3] c) Substances in Table C[6]	1. Tattoo inks shall not be placed on the market if they contain: a. the following substances in concentrations greater than the relevant generic concentration limit in Part 3 of Annex VI of Regulation (EC) No 1272/2008, unless a specific concentration limit is set in Part 3 of Annex VI of Regulation (EC) No 1272/2008: i. Carcinogenic or mutagenic substances, category 1A, 1B, or 2, excluding those substances classified only with the hazard statements H350 (inhalation) (May cause cancer by inhalation), H351 (inhalation) (Suspected of causing cancer by inhalation), H340 (inhalation) (May cause genetic defects via inhalation) and H341 (inhalation) (Suspected of causing genetic defects by inhalation) ii. Substances that are toxic to reproduction, category 1A, 1B and 2 iii. Skin corrosive or irritant and substances, category 1, 1A, 1B, 1C, and 2[9] iv. Serious eye damage/eye irritants , category 1 and 2[9] b. skin sensitisers in excess of 0.01% w/w for category 1A and 0.1% for category 1 or 1B. These provisions shall apply unless the substances are included in paragraph 2. In the event a substance is subject to more than one of the conditions in paragraphs 1.a) and 1.b), the stricter condition applies. 2. Tattoo inks shall not be placed on the market if they contain the substances listed in Table A[3], exceeding the specified concentration limits, or polycyclic-aromatic hydrocarbons (PAH), classified as carcinogenic or mutagenic categories 1A, 1B and 2 in individual concentrations exceeding 0.00005% w/w. 3. Unless already specified in paragraphs 1 or 2, tattoo inks shall not be placed on the market if they contain the substances in: a. Table C[6] in concentrations exceeding 0.1 % w/w and b. Table D[7] in concentrations exceeding 0.1 % w/w.

[6] Table C contains substances in Regulation (EC) 1223/2009 as of July 2017 prohibited for use in cosmetic products, i.e., Annex II.

[9] The concentration limit applies to each individual substance.

d) Substances in Table D[7] e) Substances in Table E[8]	4. Unless already specified in paragraphs 1 to 3, tattoo inks shall not be placed on the market if they do not meet the conditions for the substances in Table E.[8] 5. By way of derogation: a) paragraph 3 shall not apply to substances (colourants) listed in Table B or b) paragraph 1 shall not apply to substances that are gases at standard temperature and pressure.[10] 6. Tattoo inks not meeting the requirements specified in paragraphs 1 to 5 shall not be used in tattoo procedures. 7. The person responsible for the placing on the market of a tattoo ink shall ensure that the label provides the following information: a. The intended use of the mixture as a tattoo ink; b. A reference number to uniquely identify the batch; c. The name of all substances used in the tattoo ink classified for human health in accordance with Annex I of Regulation 1272/2008 but not covered by the current restriction entry, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; d. The name of any additional substances covered by this restriction entry that are used in the tattoo ink, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; e. The phrase "Contains nickel. Can cause allergic reactions." if the tattoo ink contains nickel below the concentration limit specified in Table A. f. The phrase "Contains chromium (VI). Can cause allergic reactions." if the tattoo ink contains chromium (VI) below the concentration limit specified in Table A. g. Any relevant instructions for use, unless this duplicates a precautionary statement already required to be stated on the label by Regulation (EC) No 1272/2008. The labelling shall be clearly visible, easily legible and appropriately durable. The label shall be written in the official language(s) of the Member State(s) where the substance or mixture is placed on the market, unless the Member State(s) concerned provide(s) otherwise. Where necessary because of the size of the package, the labelling information shall be included in the instructions for use.

[7] Table D contains substances in Regulation (EC) 1223/2009 as of July 2017 on Annex IV allowed for use in cosmetic products with conditions in column g: i) Colouring agents in cosmetic products intended to be applied in the vicinity of the eyes, in particular eye make-up and eye make-up remover, ii) Colouring agents in cosmetic products intended not to come into contact with the mucous membranes, iii) Colouring agents allowed exclusively in cosmetic products intended to come into contact only briefly with the skin (rinse-off products).

[8] Table E contains substances in Regulation (EC) 1223/2009 as of July 2017 in Annex IV allowed in cosmetic products with conditions in columns h to i of that Annex (e.g., purity requirements, maximum allowed concentrations of the substances themselves or their constituents). These substances can be used in tattoo inks if the conditions in Annex IV of the CPR (and transferred in Table E) are met.

[10] I.e., substances which are gaseous at temperature of 20°C and standard pressure of 101.3 kPa, or generate a vapour pressure of more than 300 kPa at temperature of 50°C.

	The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure. 8. Definitions for the purpose of this restriction entry a. Tattoo ink is a mixture consisting of colourants and auxiliary ingredients administered by intentional intradermal injection whereby a permanent skin marking or design (a "tattoo" or "permanent make-up") is made. b. Tattoo procedure (also referred to as permanent make-up, microblading, cosmetic tattooing, micropigmentation) is any intentional introduction of tattoo ink into human skin. 9. The restriction shall apply one year after its entry into force.

Note: Supplementary Table A is included in Table 4 and Supplementary Table B in Table 5 of the Background document. Supplementary Table C, D and E are included in Appendix 1 of the Background document.

A.1. THE OPINION OF RAC

RAC has formulated its opinion on the proposed restriction based on an evaluation of information related to the identified risk and to the options identified to reduce that risk as documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document.

RAC considers that the restriction proposed by the Dossier Submitter on **substances used in tattoo inks and permanent make-up** *is the most appropriate Union wide measure* to address *the identified risk in terms of the effectiveness, in reducing the risk, practicality and monitorability as demonstrated in the justification supporting this opinion, provided that the scope and conditions are modified, as proposed by RAC*.

The conditions of the restriction proposed by RAC are:

Table 3. RAC modified Restriction Option 1

a) Substances in Part 3 of Annex VI to Regulation (EC) 1272/2008 classified as: – carcinogenic, mutagenic, or toxic to reproduction category 1A, 1B, or 2 – skin sensitiser, category 1, 1A or 1B – skin corrosive or irritant, category 1, 1A, 1B, 1C, or 2	1. Tattoo inks shall not be placed on the market if they contain the substances below, unless a concentration limit is specified under paragraph 2. In the event a substance is subject to more than one of the conditions in paragraphs 1.a) to 1.c), the stricter condition applies: a. Carcinogenic or mutagenic substances, category 1A, 1B or 2 in concentration greater than 0.00005 % w/w, excluding those substances classified only with the hazard statements H350 (inhalation) (May cause cancer by inhalation), H351 (inhalation) (Suspected of causing cancer by inhalation), H340 (inhalation) (May cause genetic defects via inhalation) and H341 (inhalation) (Suspected of causing genetic defects by inhalation); b. Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009 in concentration greater than 0.00005 % w/w; c. Substances in Annex IV of Regulation (EC) 1223/2009 in concentration greater than 0.00005 % w/w with the following conditions in column g of that Annex: • Rinse-off products

– serious eye damage/eye irritation, category 1 or 2 b) Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009 c) Substances on Annex IV of Regulation (EC) 1223/2009 that are subject to conditions in columns g to i of that Annex d) Substances in Table A[3]	• Not to be used in products applied on mucous membranes • Not to be used in eye products. d. Skin sensitisers, category 1, 1A and 1B in concentration greater than 0.001 % w/w, unless a concentration limit is specified under paragraph 2; e. Skin corrosive or irritant substances, category 1, 1A, 1B, 1C, and 2 and serious eye damage/ eye irritant substances, category 1 and 2, in concentrations greater than 0.01 % w/w;[11] f. Toxic to reproduction Category 1A, 1B or 2 in concentrations greater than 0.001 % w/w. 2. Tattoo inks shall not be placed on the market if they contain substances listed in Table A,[12] exceeding the specified concentration limits. 3. By way of derogation paragraph 1 does not apply to substances that are gases at standard temperature and pressure.[13] 4. Substances in Annex IV of Regulation (EC) 1223/2009 allowed in cosmetic products (except those in paragraph 1.c) are also allowed in tattoo inks, subject to the conditions in columns h to i of that Annex, unless a lower concentration limit is specified in paragraphs 1 and 2. 5. Tattoo inks not meeting the requirements specified in paragraphs 1 to 4 shall not be used in tattoo procedures. 6. The person responsible for the placing on the market of a tattoo ink shall ensure that the label provides the following information: a. The intended use of the mixture as a tattoo ink; b. A reference number to uniquely identify the batch; c. The name of all substances used in the tattoo ink classified for human health in accordance with Annex I of Regulation 1272/2008 but not covered by the current restriction entry, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; d. The name of any additional substances covered by this restriction entry that are used in the tattoo ink, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; e. The phrase "Contains nickel. Can cause allergic reactions." if the tattoo ink contains nickel below the concentration limit specified in Table A; f. The phrase "Contains chromium. Can cause allergic reactions." if the tattoo ink contains chromium (VI) below the concentration limit specified in Table A; g. Any relevant instructions for use, unless this duplicates a precautionary statement already required to be stated on the label by Regulation (EC) No 1272/2008. The labelling shall be clearly visible, easily legible and appropriately

[11] The concentration limit applies to each individual substance.

[12] Table A contains methanol, PAHs, other impurities listed in Table 3 of CoE ResAP(2008)1, PAAs, and azo dyes.

[13] Substances which are gaseous at temperature of 20° C and standard pressure of 101.3 kPa, or generate a vapour pressure of more than 300 kPa at temperature of 50° C.

	durable. The label shall be written in the official language(s) of the Member State(s) where the substance or mixture is placed on the market, unless the Member State(s) concerned provide(s) otherwise. Where necessary because of the size of the package, the labelling information shall be included in the instructions for use. The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure. 7. Definitions for the purpose of this restriction entry a. Tattoo ink is a mixture consisting of colourants and auxiliary ingredients administered by intentional intradermal injection whereby a permanent skin marking or design (a "tattoo" or "permanent make-up") is made. b. Tattoo procedure (also referred to as permanent make-up, microblading, cosmetic tattooing, micropigmentation) is any intentional intradermal injection of tattoo ink into human skin. 8. The restriction shall apply one year after its entry into force.

Note: Supplementary Table A to the RAC modified RO1 is in Appendix 1 of this opinion.

A.2. THE OPINION OF SEAC

SEAC has formulated its opinion on the proposed restriction based on an evaluation of the information related to socio-economic impacts documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document. SEAC considers that the proposed restriction on **substances used in tattoo inks and permanent make-up**[6] is the most appropriate Union wide measure to address the identified risks, as concluded by RAC, taking into account the proportionality of its socio-economic benefits to its socio-economic costs provided that the scope or conditions are modified, as proposed by RAC and SEAC, as demonstrated in the justification supporting this opinion.

The conditions of the restriction proposed by SEAC are:

Table 4. SEAC modified RO1 (in accordance with RAC modified RO1)

a) Substances in Part 3 of Annex VI to Regulation (EC) No 1272/2008 classified as: – carcinogenic, mutagenic, or toxic to reproduction category 1A, 1B, or 2 – skin sensitising,	1. Tattoo inks shall not be placed on the market if they contain the substances specified below, unless a concentration limit is specified under paragraph 2. In the event a substance is subject to more than one of the conditions in paragraphs 1.a) to 1.c), the stricter condition applies: g. Carcinogenic or mutagenic substances, category 1A, 1B or 2 in concentration greater than 0.00005 % w/w, excluding those substances classified only with the hazard statements H350 (inhalation) (May cause cancer by inhalation), H351 (inhalation) (Suspected of causing cancer by inhalation), H340 (inhalation) (May cause genetic defects via inhalation) and H341 (inhalation) (Suspected of causing genetic defects by inhalation); h. Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009 in concentration greater

– category 1, 1A or 1B skin irritant or corrosive, category 1A, 1B, 1C, or 2 – eye damaging and irritant, category 1 or 2 b) Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009 c) Substances on Annex IV of Regulation (EC) 1223/2009 that are subject to conditions in columns g to i of that Annex d) Substances in Table A[3]	than 0.00005 % w/w; i. The following substances in Annex IV of Regulation (EC) 1223/2009 in concentration greater than 0.00005 % w/w with the following conditions in column g of that Annex: • Rinse-off products • Not to be used in products applied on mucous membranes • Not to be used in eye products. j. Skin sensitising substances, category 1, 1A and 1B in concentration greater than 0.001 % w/w, unless a concentration limit is specified under paragraph 2; k. Skin irritant or corrosive substances, category 1A, 1B, 1C, and 2 and eye damaging and irritant substances, category 1 and 2, in concentrations greater than 0.01 % w/w;[14] l. Toxic to reproduction Category 1A, 1B or 2 in concentrations greater than 0.001 % w/w. 9. Tattoo inks shall not be placed on the market if they contain substances listed in Table A,[15] exceeding the specified concentration limits. 10. By way of derogation: a. paragraph 1 does not apply to substances that are gases at standard temperature and pressure with the exception of formaldehyde.[16] b. paragraphs 1b and 1c do not apply to Pigment Blue 15:3 (CI 74160, EC 205-685-1, CAS 147-14-8) and Pigment Green 7 (CI 74260, EC215-524-7, CAS 1328-53-6) for two years after the date specified in paragraph 8 11. Substances in Annex IV of Regulation (EC) 1223/2009 allowed in cosmetic products (except those in paragraph 1.c) are also allowed in tattoo inks, subject to the conditions in columns h to i of that Annex, unless a lower concentration limit is specified in paragraphs 1 and 2. 12. Tattoo inks not meeting the requirements specified in paragraphs 1 to 4 shall not be used in tattoo procedures. 13. The person responsible for the placing on the market of a tattoo ink shall ensure that the label provides the following information: a. The intended use of the mixture as a tattoo ink; b. A reference number to uniquely identify the batch; c. The name of all substances used in the tattoo ink classified for human health in accordance with Annex I of Regulation 1272/2008 but not covered by the current restriction entry, unless the name is already required to be stated on the label by Regulation (EC) No 1272/2008; d. The name of any additional substances covered by this restriction entry that are used in the tattoo ink, unless the name

[14] The concentration limit applies to each individual substance.

[15] Table A contains methanol, PAHs, other impurities listed in Table 3 of CoE ResAP(2008)1, PAAs, and azo dyes.

[16] Substances which are gaseous at temperature of 20° C and standard pressure of 101.3 kPa, or generate a vapour pressure of more than 300 kPa at temperature of 50° C.

	is already required to be stated on the label by Regulation (EC) No 1272/2008; e. The phrase "Contains nickel. Can cause allergic reactions." if the tattoo ink contains nickel below the concentration limit specified in Table A; f. The phrase "Contains chromium (VI). Can cause allergic reactions." if the tattoo ink contains chromium (VI) below the concentration limit specified in Table A; g. Any relevant instructions for use, unless this duplicates a precautionary statement already required to be stated on the label by Regulation (EC) No 1272/2008. The labelling shall be clearly visible, easily legible and appropriately durable. The label shall be written in the official language(s) of the Member State(s) where the substance or mixture is placed on the market, unless the Member State(s) concerned provide(s) otherwise. Where necessary because of the size of the package, the labelling information shall be included in the instructions for use. The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure. 14. Definitions for the purpose of this restriction entry a. Tattoo ink is a mixture consisting of colourants and auxiliary ingredients administered by intentional intradermal injection whereby a permanent skin marking or design (a "tattoo" or "permanent make-up") is made. b. Tattoo procedure (also referred to as permanent make-up, microblading, cosmetic tattooing, micropigmentation) is any intentional intradermal injection of tattoo ink into human skin. 15. The restriction shall apply one year after its entry into force.

Note: Supplementary Table A to the RAC/SEAC modified RO1 is in Appendix 1 of this opinion.

B. JUSTIFICATION FOR THE OPINION OF RAC AND SEAC

B.1. IDENTIFIED HAZARD, EXPOSURE/EMISSIONS AND RISK

Justification for the opinion of RAC

B.1.1. Description of and justification for targeting of the information on hazard(s) and exposure/emissions) (scope)

B.1.1.1. Summary of proposal:

Tattoo[17] inks are mixtures of colourants[18] and auxiliary ingredients (such as surfactants, binding agents, fillers). They can be injected into the dermis or other parts of the body (e.g., in parts of the eye, under the tongue, in mucous membranes) of consumers to create long-lasting design or marking used to decorate the skin or to enhance body features (e.g., to create permanent make-up or PMU). The pigments used in tattoo inks are not specifically produced for such purposes, i.e., intradermal injection into the human body. They are often of low purity and can contain, intentionally or as an impurity, a large number of hazardous substances. Polycyclic aromatic hydrocarbons (PAH), primary aromatic amines (PAA), and heavy metals were respectively detected in 43, 14 and 9 percent of the samples analysed in one report (JRC, 2016b).

The number of people in the EU with tattoos and permanent make-up has been increasing as well as the number of RAPEX (Rapid alert system for non-food dangerous products) notifications concerning tattoo and permanent make-up inks.

Several studies have identified human health effects due to the exposure to chemicals in tattoo inks. In a 2010 survey (Klügl et al., 2010), about 68% of tattooed people reported skin problems, such as bleeding, crusts, itching, oedema, pain, burning sensation and blister formation, and 6.6% reported systemic reactions after tattooing, including dizziness, headache, nausea or fever. After several weeks, 9% of tattooed people reported they still had health problems and 6% reported they had persistent skin symptoms, such as scarring, permanently elevated skin areas, or intermittent oedema caused by wetness or touch.

Coloured tattoo inks have been shown to be mainly responsible for the adverse skin reactions reported following persons being tattooed (Wenzel et al., 2013), with red colourants being associated with the majority of the allergic reactions (Danish EPA, 2012). Reactions can appear months or years after the tattoo was completed. This is a remarkably long period of sensitisation induction and, although the exact mechanism has not yet been elucidated, this delayed response is an indication that intradermal deposit of tattoo pigments results in lifelong exposure and can potentially have a negative effect on human health (Laux et al., 2016). Furthermore, the pigments are also known to be re-distributed in the body and have later

[17] Unless otherwise specified, a tattoo (ink) includes a permanent make-up (ink). Temporary (e.g., stickers and henna painting) and traumatic (non-intentional) tattoos are not in the scope of this assessment.

[18] Colourant is the commonly used denomination for pigments, lakes and dyes that are coloured molecules.

been found in different organs such as the lymph nodes and the liver (Sepehri et al., 2017a). In addition to local effects at the point of injection, there is clear evidence of systemic exposure, which poses a risk of other health effects including cancer and reproductive health.

Seven Member States[19] already have national legislation in place that regulates, amongst others, the chemical composition of tattoo inks based on the Council of Europe (CoE) resolution on the safety of tattoos and PMU: ResAP(2008)1 or its predecessor, ResAP(2003)2. Three other Member States have notified their intention to introduce similar legislation. For these reasons, the European Commission (COM) requested ECHA to assess the human health risk.

The Dossier Submitter reviewed the substances known to be present in tattoo inks according to the technical and scientific literature, stakeholder reviews and surveillance results, and as reported in the Safety of tattoos series of reports by the Joint Research Centre (JRC). The Dossier Submitter does not consider the available data as sufficiently reliable and comprehensive to base a restriction on in terms of individual substances present in the majority of inks. The review by the Dossier Submitter illustrated that there are a high number of substances used in tattoo inks, many of which are unknown and of the ones known, there is often insufficient information on concentrations and/or hazard data to allow a quantitative assessment of their risks. Moreover, an approach that lists and restricts individual substances would have the disadvantage of not capturing all hazardous substances (including the substantial number of substances that may act as substitutes). Therefore, it is proposed to restrict all substances with certain specific hazards in tattoo inks or those restricted in existing legislation, based on the argumentation that these hazards are severe enough to justify the proposal. This is also the approach used in national legislation based on the Council of Europe resolution. The groups of substances covered are:

- Substances included based on their harmonised classification(s) as:
    - carcinogenic or mutagenic (CM), categories 1A, 1B or 2. Azo colourants that are not classified as CM category 1 or 2, but may undergo decomposition to or contain residual aromatic amines that are so classified, are also included
    - toxic to reproduction, categories 1A and 1B and 2
    - skin sensitisers, skin corrosives, skin or serious eye damage or irritants.
- Substances included in the restriction based on their inclusion in the Cosmetic Products Regulation (CPR), i.e., substances:
    - on Annex II of the CPR (the list of substances prohibited in cosmetic products)
    - on Annex IV of the CPR (positive list of colourants allowed in cosmetic products with some use or concentration restrictions).
- Substances included in the restriction based on the CoE resolution (and national legislation) and not considered in the previous categories:
    - 5 substances in Table 3 of ResAP(2008)1

[19] Belgium, France, Germany, Netherlands, Spain, Sweden and Slovenia.

- 14 colourants in Table 2 of ResAP(2008)1 without harmonised classification and not included in point 1 above.

In total, more than four thousand substances fall within the scope of this restriction proposal (in the categories described above).

B.1.1.2. RAC conclusion(s):

RAC is of the opinion that substances which are known to have intrinsic properties leading to serious health hazards should be restricted in tattoo inks. These properties include:

- carcinogenicity, mutagenicity, reproductive toxicity, skin sensitisation, corrosion or significant irritation of skin or eye as indicated by their harmonised EU classification, or
- properties, which were the cause to restrict them in existing relevant legislation:
  - on the list of substances prohibited in cosmetic products or allowed to be used in cosmetic products but with use or concentration restrictions (Annex II and IV of the Cosmetic Product Regulation (EC) No 1223/2009), or
  - by the Council of Europe resolutions on requirements and criteria for the safety of tattoos and permanent make-up, which has been the basis for national legislation in several members states in the EEA.

B.1.1.3. Key elements underpinning the RAC conclusion:

RAC agrees with the Dossier Submitter that tattooing or permanent make up procedures can lead to local and systemic health effects in humans, and that tattoo inks can and do contain substances of concern, as detailed above. . The tattoo ink market represents only a tiny fraction of the global production of colourants. The pigments used in tattoo inks are not specifically produced for such purposes, nor are they specifically developed[20] to be injected under the skin. They can lack the high purity standards and contain levels of hazardous substances that are not appropriate for injecting into the human skin (JRC, 2015b). Therefore, to limit the potential health risk, substances known or suspected to cause adverse health effects should be restricted in tattoo inks. This may apply to colourants (i.e., pigments (inorganic) and dyes (organic)), impurities and other auxiliary ingredients of the inks.

RAC agrees with the approach taken by the Dossier Submitter to include hazardous substances that have not yet been detected in tattoo inks in the scope of the restriction, recognising that the majority of these chemicals (more than 4 000 in total) have not yet been detected in tattoo inks, but agrees that it is important to include them in the scope. This is primarily because of the absence of sufficiently reliable and comprehensive safety information regarding the substances of concern found in tattoo inks, considering their manner of use through intradermal injection. In addition, this approach is expected to prevent future use of

[20] Because the tattoo industry is small in comparison to other downstream user sectors, pigments are generally developed for e.g., buildings materials in general, plastics, coatings, printing, textiles, food, cosmetics and medical applications.

hazardous alternatives to replace the restricted substances.

RAC agrees with the conclusion of the Dossier Submitter that health risks are at least as high (or higher) when substances contained in tattoo inks are introduced into the skin compared to their application on the surface of the skin. Assessments conducted under CPR, where intradermal injection is not used, and certain substances restricted by national regulations (based on CoE ResAP(2008)1) should therefore be considered as relevant. However, RAC also notes further issues to be considered in this context as follows:

- The assumption that the health risks of injecting substances are at least as high as when applied on the skin, is not valid in all situations (as described in the Background Document, Annex E: Assumptions, uncertainties and sensitivities). For example for products which are applied topically on a daily basis throughout a lifetime, compared to tattoo ink which is applied only a limited number of times (or even only once). Although a tattoo poses a long-term exposure, the cumulative dose is expected to be lower than for a product applied daily over a lifespan[21].
- Not all inclusions in Annex II of the CPR have traceable opinions of the Scientific Committee on Consumer Safety (SCCS). Nevertheless, RAC considers that they have been previously assessed under other Union legislation and agrees with the Dossier Submitter to include these substances on this basis in the scope. This is fully in line with REACH (Annex I of REACH, para 0.5: "Where available and appropriate, an assessment carried out under Community legislation (e.g., risk assessments completed under Regulation (EEC) No 793/93) shall be taken into account in the development of, and reflected in, the chemical safety report. Deviations from such assessments shall be justified."). In addition, these substances are already included in the Council of Europe resolutions and restricted in tattoo inks by the national legislation of seven Member States.

In addition, RAC notes those substances that were not included in the proposal due to lack of information (Appendix D.1) by the Dossier Submitter. At the present moment, these substances are not in the scope of the restriction since they are not classified and not restricted by CPR Annex II, Annex IV, or CoE ResAP(2008)1. RAC considers that the Dossier Submitter's recommendation to consider these substances later through various regulatory measures, e.g., a further request by the Commission, a restriction proposal from a Member State, through harmonised classification which will bring a substance into the scope of the proposed restriction, or through the Biocidal Products Legislation[22]could add to the risk

[21] See also section B.1.2.4. *Uncertainties in the risk characterisation* for further discussion on uncertainties regarding metabolic differences between the epidermis and dermis

[22] Several substances used as preservatives, which do not have harmonised classifications as skin sensitisers, although they are known (and some of them are potent) skin sensitisers in humans (Thyssen et al., 2012), have been found in tattoo inks (e.g. methyldibromo glutaronitrile). Methylisothiazolinone (MIT) and methylchloroisothiazolinone (CMIT) are classified as skin sensitisers. Some of them have been found in concentrations reported to induce elicitation response in patch testing (e.g. Pasche and Hunziker, 1989). It is expected that they will be regulated under the Biocidal Products Regulation. For example, strong sensitisers methylchloroisothiazolinone and methylisothiazolinone are currently under review for type 6 biocidal products (Preservatives for

reduction capacity of the proposed restriction in the future.

RAC notes that this restriction proposal applies only to consumer and not to professional exposure. RAC agrees with the Dossier Submitter that the risks for tattooists are likely to be reduced by the restriction since less hazardous substances would be used.

B.1.2. Description of the risk(s) addressed by the proposed restriction

B.1.2.1. Information on hazard(s)

B.1.2.1.1. Summary of proposal:

To efficiently and effectively deal with all the substances included in the scope of this restriction, the Dossier Submitter has addressed a number of groups (where no reliable dose descriptor (e.g. a DNEL) can be set), through a qualitative approach[23] : irritation/corrosion, sensitisation, carcinogenicity and mutagenicity. A similar approach was taken for substances with a current prohibition in cosmetic products. The remaining substances in the scope are assessed in a (semi-)quantitative manner.

Therefore, the Dossier Submitter has performed the hazard assessment in the following way:

a) For the following groups of substances it is not possible to do a quantitative risk assessment due to their predominantly non-threshold effects and/or the difficulty to identify a reliable dose-descriptor and they are, therefore, assessed in a qualitative manner:

- substances with inherent properties that may cause an effect with no threshold. This is the case for most substances with carcinogenic or mutagenic classifications and lead compounds[24]. Substances only classified for carcinogenicity or mutagenicity through inhalation are exempted from the scope of the restriction (unless they are included for another endpoint).

- substances classified as skin sensitisers. When skin sensitisers are deposited into the dermis via an injection, stronger sensitisation/elicitation reactions may occur and with lower doses than when deposited on the skin. In theory, skin sensitisers might have thresholds, but data is very seldom available with which to set such a threshold.

- substances classified under CLP for skin corrosion/irritation or serious eye damage/irritation, based on the assumption that the effects will be more severe when

products during storage). On the other hand, methyldibromo glutaronitrile is not on the list of preservatives approved for use in cosmetic products since it has been shown "to cause elicitation of reactions by repeated open exposures with a rinse-off preparation at the maximum concentration allowed in rinse-off products (0.1%)" (SCCP Opinion, 2005), but it is presently approved for type 6 biocidal products (Preservatives for products during storage). Nevertheless, the above mentioned legal routes are expected to solve issues like that.

[23] REACH Annex I para 1.1.2 and ECHA Guidance R.8.

[24] For the purposes of deriving a concentration limit for lead a semi-quantitative assessment has been made.

these substances are injected into the skin rather than applied on the skin. This assumption also applies to these substances when injected into the eyes.

b) The following substances are included based on their intrinsic properties and evaluated in a (semi-)quantitative manner as either DN(M)ELs have been derived, or the substances have been grouped with other substances for which DN(M)ELs have been derived:

- Methanol, due to its classification as STOT SE based on its effects on the optic nerve and central nervous system seen after a single exposure. A DNEL of 8 mg/kg bw/day for the general population was calculated based on an OEL of 260 mg/m^3 or 200 ppm for an 8 hour exposure (Commission Directive 2006/15/EC of 7 February 2006), giving an exposure of 40 mg/kg bw/day, using an assessment factor (AF) of 5.

- Primary aromatic amines (PAAs) and azo colorants. These substances are included because: they can be found as non-reacted impurities (i.e., PAAs used in the production of azo colourants), they are potentially produced when azo colourants are degraded by sun or laser irradiation, enzymatic or bacterial effects to hazardous substances, or an assessment for the purposes of the ResAP and national legislation has shown the need for action (ResAP Table 2 substances). A hazard evaluation was performed for the ten PAAs found in a Danish survey of tattoo inks (DEPA, 2012) to determine a DMEL for the carcinogenic effects. DMELs could only be derived for two substances – aniline and o-anisidine (Table 4 in the Background Document). The lowest DMEL of 2 x 10^{-5} mg/kg bw/day (Aniline) was carried forward by the Dossier Submitter in the risk assessment for PAAs. For the azo colourants a practical approach was chosen by the Dossier Submitter. A minimum concentration of azo colourants of 5-10% in the tattoo ink is normally required to be able to colour the skin. Thus, a practical limit of 0.1% will prevent the use of the specifically identified azo colourants that are in the scope of the restriction[25].

- Substances classified for reproductive toxicity in hazard categories 1A, 1B and 2

The Dossier Submitter used a quantitative approach to demonstrate risk and to derive concentration limits for substances toxic to reproduction in tattoo inks and PMUs as, traditionally, these substances have been assumed to have an individual threshold level below which no adverse effect is expected. In line with this, dose descriptors (NOAEL/LOAEL) were identified from available studies and DNELs were derived in accordance with ECHA guidance R.8.[26] The assessment focused on substances which are only classified as Repro 1A/B (and not Carc. or Muta. or Skin Sensitiser) and for which there is available information for risk assessment. As a result, the $DNEL_{\text{general population, reproductive effects}}$ for 27 reprotoxic substances

[25] Any azo colourants classified as C and M or on Annex II of CPR will also be in the scope of the restriction.

[26] Some of the substances that were assessed are known to have endocrine disrupting properties, e.g., phthalates. Nevertheless, the Dossier Submitter assessed reproductive toxicity as a threshold endpoint in this restriction proposal, as this will indicate a minimum level of risk where the concern may be higher if there was no threshold due to any ED effects.

categories 1A and B were derived. The overall $DNELs_{general\ population,\ reproductive\ effects}$ of 0.001 mg/kg bw/day (for (R)- and (S)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrone based on a LOAEL of 0.04 mg/kg bw/day and an overall AF of 30) is proposed as the most sensitive DNEL for risk assessment of reprotoxic substances in tattoo inks.

- Certain substances listed on Table 3 of the CoE ResAP(2008)1 considered to be impurities in tattoo inks.

Table 3 in the CoE ResAP(2008)1 is a list of maximum allowed concentrations of impurities in products for tattoos. For substances where the Dossier Submitter had information that the concentration limits necessary to adequately control the risk differ from those specified in CoE ResAP, a (semi-)quantitative assessment was performed, and DN(M)ELs were derived. These include: arsenic, barium, copper, lead and zinc. The Dossier Submitter proposes to include the remaining substances on Table 3 of ResAP in the scope of the restriction, as assessments under national legislation of seven Member States national restrictions and Table 3 of ResAP have concluded that these concentration limits are necessary to control risk.

Table 5. DN(M)ELs derived for selected substances on the CoE ResAP(2008)1, Table 3

Substance	**DMEL, general population, carcinogenic effects or DNEL STOT-RE**
Arsenic (As)	DMEL 0.0005882 µg/kg bw/day
Barium (Ba)*	DNEL 0.60 mg/kg bw/day
Copper (Cu)*	DNEL 0.037 mg/kg bw/day
Lead (Pb)	DMEL 0.05 µg/kg bw/day
Zinc (Zn)*	DNEL 0.166 mg/kg bw/day

* Soluble

c) Substances included based on prohibition from use in the Cosmetic Products Regulation (CPR) or subject to special conditions

Qualitative assessment was used to demonstrate hazard and risk for the following substances in accordance with paragraph 0.5 of Annex I of REACH:

- substances on Annex II of the Cosmetics regulation (list of substances prohibited in cosmetic products).
- substances on Annex IV to the Cosmetics regulation that are not allowed to be used in contact with mucous membranes, eyes or in prolonged contact with the skin (column "g") or subject to other conditions specified in columns "h" to "i" of the Annex (e.g., purity requirements).

The Dossier Submitter assumes that the intrinsic properties will manifest themselves to a higher degree when injected into the dermis in a tattoo than if applied on the body via cosmetic products.

B.1.2.1.2. RAC conclusion(s):

RAC supports the Dossier Submitter approach regarding the methods used for risk

assessment and agrees that all substances covered by this restriction may in practice be divided in terms of hazard and risk assessment into four groups as follows:

1. Substances with predominantly non-threshold health hazards, for which health risk can only be evaluated in a qualitative manner (carcinogens, mutagens, lead compounds, skin sensitisers, skin and eye irritant or corrosive substances)
2. Substances with non-threshold health hazards, for which a health risk can be evaluated in a qualitative manner but for which the concentration limit is derived in a quantitative manner using DMELs (primary aromatic amines (PAAs).
3. Substances with predominantly threshold health hazards, for which a health risk can be evaluated in a quantitative manner with a derivation of DNELs (methanol, reproductive toxicants, some substances considered to be impurities in tattoo inks, listed in table 3 of the CoE ResAP(2008)1)
4. Substances included in the scope of the proposed restriction based on a prohibition of their use in the CPR or because the substance is subject to special conditions in the CPR.

RAC considers that all relevant health hazard classes are covered by the Dossier Submitters proposal, and agrees, in general, with the hazard assessment for the substances or group of substances as evaluated by the Dossier Submitter. However, in certain cases (PAAs, barium, copper, reprotoxic substances), a deviation from Dossier Submitter's derived DNELs/DMELs is proposed by RAC.

Regarding the hazards assessment of derogated substances, RAC agrees with the Dossier Submitter's proposal to exclude substances classified for the inhalation route only from the scope.[27] In addition, RAC supports the modified proposal to exempt substances that are gases at standard temperature and pressure, considering hazards posed by inhalation route only not relevant for intradermal exposure to tattoo ink.

B.1.2.1.3. <u>Key elements underpinning the RAC conclusion(s):</u>

The information used for the assessment was retrieved by the Dossier Submitter from the published literature, databases and REACH registrations in accordance with ECHA guidance on information-gathering. RAC notes that the placing on the market for use by the general public of many of the substances covered in the scope of this restriction is already limited or prohibited by other EU regulations (e.g. REACH Annex XVII (entries 28-30)), EU Member States regulations on tattoo inks, or by the CLP Regulation. This indicates that hazards and risks posed by these substances have already been assessed to a great extent. RAC also agrees that some of the substances covered by resolutions of the Council of Europe on requirements and criteria for the safety of tattoos and permanent make-up are also relevant and should be included in the restriction.

The Dossier Submitter considered all relevant health hazard classes listed in the CLP

[27] ECHA Guidance on the Application of the CLP Criteria (Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 4.1, 2015) explains that the hazard statement allows for identifying the route of exposure 'if it is conclusively proven that no other routes of exposure cause the hazard' (CLP Annex I, Table 3.6.3), and that genotoxic carcinogens are generally suspected to be carcinogenic by any route.

Regulation, but prioritised some (see Figure 1 in the Background Document) due to the extensive number of substances intended to be covered by the scope.

The substances having harmonised classification for the following hazard classes have been considered, and, when justified, included in the scope of the restriction:

- **acute toxicity/STOT SE** – The Dossier Submitter considered it difficult to group all the substances with harmonised acute toxicity and STOT SE classifications as they give rise to very diverse health risks. Therefore, only methanol is included in the scope, as it is the only substance with STOT SE classifications (effects on the optic nerve and central nervous system) found to be present in tattoo inks and not covered by other groups or individual assessments.
- **STOT RE** – No substance is proposed to be restricted according to this hazard class. Only one STOT RE substance in tattoo inks was identified that was not covered by other groups or individual assessments: Uranium; however is within the scope of Council Directive 96/29/Euratom as a radioactive substance and therefore, exempted from REACH.
- **skin corrosivity/irritant, severe eye damage/ irritant, skin sensitisation, germ cell mutagenicity and carcinogenicity** – The Dossier Submitter proposed all substances with harmonised classifications for these hazard classes to be restricted with general or specific concentration limits.
- **reproductive toxicity** – All reprotoxic substances in tattoo inks (based on a quantitative hazard assessment approach) with a general concentration limit.

In addition, the Dossier Submitter proposed to include in the scope:

- **azo colourants** that by sunlight or laser irradiation, enzymatic or bacterial effects, decompose to primary aromatic amines with harmonised classification for carcinogenicity, mutagenicity or skin sensitisation, and those for which an assessment for the purposes of the CoE ResAP and national legislation has shown the need for action. As the decomposition products can be expected to be carcinogenic, mutagenic or skin sensitising, they are included in the qualitative assessment for those substances with specific or generic concentration limits;
- **impurities in products for tattoos and PMU listed in Table 3 in the CoE ResAP(2008)1**, since an assessments under CoE ResAP and national legislation of seven Member States have concluded that these substances should be restricted in tattoo inks in order to control human health risks; and
- substances were also included based on their **prohibition from use in the CPR** or subject to special conditions, since it is assumed that the intrinsic properties will manifest themselves to a higher degree when injected into the dermis in a tattoo than if applied on the body via cosmetic products.

RAC notes that there is large overlap of the substances in these last three groups and those included in the scope due to their harmonised classification.

RAC agrees with this approach, noting that more than 6 000 substances were initially considered in the Dossier Submitter evaluation, agrees that the prioritisation performed by

the Dossier Submitter was necessary and rational.

However, RAC recognises that the process of prioritisation leads to unquantifiable and significant uncertainties due to:

- the assessment of hazardous substances that have not yet been detected in tattoo inks (since among the large number of substances used in tattoo inks, there are many that are still not known to regulators, and since this approach is expected to prevent future use of hazardous alternatives to restricted substances), and
- the assumption that the intrinsic properties will manifest themselves to the same or higher degree when substances in tattoo inks are injected into the skin compared to application on the skin, although it does not always have to be the case (as described in the Background Document, Annex E. Assumptions, uncertainties and sensitivities).

RAC supports the approach taken by the Dossier Submitter to differentiate between the different approaches to the risk assessments (and the derivation of concentration limits) to fully reflect the types of health hazards of the substances concerned and the available data on them.

RAC accepts that all substances covered by this restriction may be divided in terms of hazard and risk assessment as follows:

1. Substances with predominantly non-threshold health hazards or for which it is difficult to identify a reliable dose-descriptor, for which the health risk was evaluated in a **qualitative manner** (carcinogens, mutagens, lead compounds, skin sensitisers, skin and eye irritant or corrosive substances);
2. Substances with non-threshold health hazards, for which the **risk** was **qualitatively assessed** by the Dossier Submitter but a **concentration limit** was **derived quantitatively** through a **DMEL** (PAAs);
3. Substances with predominantly threshold health hazards, for which the health risk was evaluated in a **quantitative manner** with the derivation of DNELs (methanol, reproductive toxicants, substances considered to be impurities in tattoo inks, listed in table 3 of the CoE ResAP(2008)1); and
4. Substances included in the scope of the restriction based on prohibition from use in the Cosmetic Products Regulation or subject to special conditions, for which the health risk was evaluated in a **qualitative manner**.

Analysis of health hazards posed by substances in tattoo inks[28]

Details of the hazard assessments of substance groups and individual substances are given in Appendix 3 of the opinion, while derivation of concentration limits is described in Appendix 4.

1. **Substances with predominantly non-threshold health hazards evaluated qualitatively**

[28] See Appendix 3 to this opinion for more detailed explanations for each of the categories.

Carcinogenicity and mutagenicity

RAC agrees with the Dossier Submitter that for a substance possessing carcinogenic properties, the establishment of a dose-response relationship to characterise its potency requires a considerable amount of human or animal data, which is not possible to gather for the majority of them. In addition, there are no data on the carcinogenic potency of substances with harmonised classifications specifically following the intradermal route of exposure, as this is not normally used in hazard identification. Therefore, RAC agrees it is reasonable to apply a qualitative approach for the characterisation of dose/concentration-response for human health.

Skin sensitisation

For this endpoint a qualitative approach was chosen by the Dossier Submitter. Although skin sensitisers theoretically might have thresholds, data is very rarely available to build a dose-response or set a reliable threshold. RAC agrees with the Dossier Submitter that a DNEL could not be set for this hazard endpoint and a qualitative approach is therefore supported.

Skin and eye irritant/corrosion

RAC considers that it is unlikely that all local skin reactions are allergic in nature or due to a tattooing procedure only, and agrees with the Dossier Submitter that some of the reactions can be irritative in nature[29]. RAC supports the Dossier Submitter's approach regarding a qualitative risk assessment.

2. **Substances with non-threshold health hazards evaluated qualitatively and concentration limits set quantitatively (DMELs)**

The Dossier Submitter qualitatively assessed the risk from this group of substances. In these cases a reliable dose descriptor could not be set as the substances are either carcinogens or mutagens (PAAs), are assumed to decompose to CM substances (azo colourants), or have non-threshold neurodevelopmental effects (lead).

RAC also agrees with the Dossier Submitter that it is not possible to introduce an enforceable ban of all hazardous substances in tattoo inks. Therefore, in some cases there was a need for setting a concentration limit for hazardous substances and impurities in tattoo inks to protect the consumers from adverse health effects (see section B.1.2). The concentration limits in the Dossier Submitters proposal for this group of substances were based on the DMELs for these substances. To derive the DMEL values for non-threshold carcinogenic substances, the maximum level of indicative tolerable lifetime excess cancer risk for consumers was assumed to be 10^{-6}, in accordance with ECHA guidance R.8.1.1 (ECHA, 2012).

Azo colourants and primary aromatic amines (PAAs)

Azo colourants are important colourants in tattooing, comprising more than 50% of the colourants used (mainly in red, yellow and orange tattoo inks) (JRC, 2015b), and therefore,

[29] According to clinical criteria set by Serup, et al. (2015b), 13% of 493 tattoo reactions (reported by patients at the "Tattoo Clinic" at the Department of Dermatology at Bispebjerg University Hospital, Copenhagen) were classified as non-allergic, inflammatory, non-infectious reactions.

they have been specifically addressed by the Dossier Submitter.

Primary aromatic amines (PAAs) might be present in tattoo inks as impurities (e.g., as non-reacted remnants in the final azo colourant), as products of ultraviolet decomposition (sunlight or laser light), or enzymatic or bacterial decomposition of azo colourants, or could be added to an azo colourant for achieving a specific nuance of a colour.

Hazard assessment of azo colourants

Azo colourants are of low acute toxicity (Bafana et al., 2011), and most of them do not have harmonised classification. Nevertheless, some of them are classified for carcinogenicity and skin sensitisation, and, as already mentioned in the previous section (*Hazard assessment of PAAs*), some of them may decompose to PAAs of concern, either by ultraviolet (sunlight or laser light), enzymatic or bacterial degradation.[30]

RAC agrees with the Dossier Submitter to include in the scope **azo colourants** that:

- could decompose via amide hydrolysis into PAAs with carcinogenic, mutagenic or skin sensitising properties (21 out of the 67 azo colourants with information that they can be found in tattoo inks, JRC, 2015b); or
- are based on 3,3'-dichlorobenzidine, and could form 3,3'-dichlorobenzidine during photo-decomposition (7 out of 67 analysed azo colourants); or
- have a scientific evaluation by Scientific Committee on Consumer Products (SCCP, now Scientific Committee on Consumer Safety, SCCS), stating that they may release one or more carcinogenic aromatic amines (4 azo colourants).

RAC also agrees with the Dossier Submitter's proposal to include 16 azo colourants listed in table 2 of the CoE ResAP(2008)1 into the scope.

Hazard assessment of PAAs

RAC agrees with the Dossier Submitter to choose carcinogenicity and skin sensitisation as the most sensitive endpoints for hazard assessment of PAAs, and carcinogenicity for risk assessment and setting of concentration limit. The Dossier Submitter proposed to set risk-based concentration limit for **29 PAAs**. RAC agrees with the Dossier Submitter's proposal, including the proposal to set specific concentration limit also for PAAs restricted in REACH that have not yet been found in tattoo inks. This approach aims to prevent substitution to other azo colourants that may also decompose to these PAAs.

RAC does not agree with the Dossier Submitter to exclude the two PAAs from Table 1 of CoE ResAP(2008)1 (6-amino-2-ethoxynaphthaline CAS 293733-21-8 and 2,4-xylidine EC 202-440-0 / CAS 95-68-1). RAC proposes to carry forward to the risk characterisation of PAAs a

[30] Colourants used in tattoo inks are generally not produced for the purpose of tattooing, but for applications (e.g. paints for textiles, cars and plastics) for which sterility is not necessarily required. Therefore, biological degradation and PAAs formation can happen during storage (DEPA, 2017c).

DMEL value of 4 x 10^{-5} mg/kg bw per day for o-anisidine as a proxy for all PAAs.[31]

Substances considered to be impurities in tattoo inks, listed in table 3 of the CoE ResAP(2008)

In Table 3 of CoE ResAP(2008)1, maximum allowed concentrations are set for 13 elements, benz-a-pyrene and olycyclic aromatic hydrocarbons (PAHs)), all impurities in tattoo inks.

The Dossier Submitter has individually assessed some of these substances to determine the need for risk-based concentration limits in tattoo inks. Five elements (see below) have been assessed to reflect the conclusions of recent risk assessments and due to their presence in some colours of tattoo inks. For the remaining substances, except PAHs and nickel, the same CLs as in the Table 3 of the CoE ResAP(2008)1 are proposed as technically achievable limits.

Hazard and risk assessment for the five elements (arsenic, barium, copper, lead and zinc) is described separately for those assessed by a semi-quantitative approach (lead and arsenic), and for those assessed by a quantitative approach (barium, copper and zinc).

Lead

The critical health effects of lead include the effects on the nervous, haematopoietic and reproductive systems, and the carcinogenic effect. The most critical effect of lead at low concentrations was considered to be the effects on the developing nervous system. RAC considers that a value of 0.05 µg/kg bw/day is appropriate for use as a DMEL in the risk characterisation, as proposed by the Dossier Submitter.

Arsenic

Arsenic is listed in Table 3 in the CoE ResAP(2008)1 as an impurity with maximum allowed concentration of 2 ppm (0.0002%) in tattoo inks. Arsenic compounds are also included in the list of substances prohibited in cosmetic products under Annex II of the CPR. The Dossier Submitter based their evaluation on the RAC opinions establishing a reference dose response relationship for carcinogenicity of inorganic arsenic compounds (in the framework of authorisation process)[32] and on the evaluation of the occupational exposure limits (OELS) for arsenic acid and its inorganic salts, particularly with reference to its carcinogenicity.[33]

RAC agrees with the Dossier Submitter to consider carcinogenicity as the most sensitive outcome. RAC agrees with the Dossier Submitter's approach: to base the hazard assessment on previous RAC opinions (ECHA, 2013; ECHA, 2017), i.e. to choose carcinogenicity as the most sensitive outcome, and to apply linear dose-response curve for lung tumours, based on

[31] DMEL value for aniline of approximately 2 x 10^{-5} mg/kg bw/day derived by the Dossier Submitter has been corrected by RAC to 4.6 x 10^{-5} mg/kg bw/day. Since SCOEL set TWA for aniline based on a MoA-based threshold (methaemoglobinaemia), while no threshold value has been used for o-anisidine, RAC proposed to carry forward to the risk characterisation of PAAs a DMEL value of 4 x 10^{-5} mg/kg bw/day for o-anisidine. For detailed justification, please see Appendix 3 of RAC opinion.

[32] ECHA, 2013. Application for authorisation – establishing a reference dose-response relationship for carcinogenicity of inorganic arsenic compounds, s.l.: ECHA risk assessment committee RAC/27/2013/07 Rev.1.

[33] ECHA, 2017. Committee for Risk Assessment (RAC) opinion on arsenic acid and its inorganic salts (29 May 2017), s.l.: European Chemicals Agency.

human data following oral exposure to arsenic in drinking water.

3. **Substances with assumed threshold health hazards**

For this group of substances health risk was evaluated in a quantitative manner with derivation of DNELs (methanol, reproductive toxicants with harmonised classification as Repr. Cat. 1A/B and 2 (Annex B.5.9 and Appendix B.3), and certain impurities in tattoo inks such as barium, copper and zinc, listed in table 3 of the CoE ResAP(2008)).

Methanol

Methanol was proposed to be included in the scope of the restriction due to its harmonised classification as STOT SE 1, based on its effects on the optic nerve and central nervous system (CNS) observed after a single exposure.

A quantitative approach was applied, with DNEL derivation based on occupational exposure level of 260 mg/m^3 (or 200 ppm) for an 8-hour exposure, giving an exposure of 2.6 g/person/day, equivalent to 40 mg/kg bw/day. RAC agrees with the Dossier Submitter's approach and the derived DNEL value.

Substances classified for toxicity to reproduction

To determine the risk from reprotoxic substances, the Dossier Submitter has assessed those reprotoxic substances which have harmonised classification as reproductive toxicants category 1 and 2, but which are not classified as carcinogenic or mutagenic or skin sensitising substances. So far only four of this group, have been found in tattoo inks: bis(2-ethylhexyl) phthalate, dibutyl phthalate, mercury and disodium tetraborate, anhydrous (JRC, 2015b). For other reprotoxic compounds, no information is available on their content in tattoo inks as an ingredient or impurity.

RAC considers that substances classified for reproductive toxicity may exert adverse effects when tattoo inks containing them are injected into dermis or other parts of the body.

RAC considered that it is appropriate to use a quantitative hazard assessment approach to demonstrate a risk and to derive concentration limits for currently known substances in tattoo inks that are classified as Repro 1A/B-.

For 27 of the 34 substances, $DNEL_{\text{general population, reproductive effects}}$ could be derived. For 96% of the substances DNEL values between 0.001 and 1 mg/kg bw/d were obtained. The "reprotoxic only" substances were considered as a group, and the lowest DNEL for this group (not including one outlier) was used by the Dossier Submitter for the risk characterisation. The lowest DNEL was for the substances (R)- and (S)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrones (warfarin) based on a LOAEL of 0.04 mg/kg bw/d and an overall AF of 30.

RAC notes that warfarin has not so far been detected in tattoo inks, therefore dibutyl phthalate (DBP), with the lowest LOAEL out of the substances known to have been detected in tattoo inks, is considered more appropriate for DNEL derivation. A LOAEL of 2 mg/kg bw/d was selected as the starting point (POD) for risk assessment. The following assessment factors were used: AF for interspecies differences: 10; AF for intraspecies differences: 10; AF due LOAEL instead of NOAEL: 3; resulting in a total AF of 300 and a DNEL of 0.007 mg/kg/day for DBP. When proposing a limit value for the group of reprotoxic substances, an additional factor

of 10 is proposed to be used to account for: mixture /cumulative effects and uncertainties, possibility of combined effects of several reprotoxicants present in tattoo inks with the same mode of action, including ED effects and the possibility that more potent substances may be present in tattoo inks with a resulting overall AF 3000. This leads to a DNEL for the group of reprotoxic substances of ≈0.0007 mg/kg bw/day.

The substances classified as category repro 2 in Annex VI of CLP have not been assessed individually due to the lack of available information.

Substances considered to be impurities in tattoo inks listed in table 3 of the CoE ResAP(2008) – quantitative assessment

Barium

Barium sulphate is used in the flocculation of organic pigments to optimise their dispersibility, as a white colour, in other colours to adjust colour strength (because of its lightening effect), and as a filler in the production of lakes[34] (JRC, 2015b). Barium salts are regulated by CPR.

The concentration limit for barium, as an impurity in tattoo inks, set by CoE ResAP(2008)1 is 50 ppm (50 mg/kg). EU market surveillance showed that 20% of tattoo ink samples had Ba levels higher than the recommended CoE limit value. The information on which basis the CoE ResAP(2008)1 limit was set is not available.

The Dossier Submitter evaluated the available toxicological data (from ECHA registration dossiers and database searches) for the barium pigments/compounds found in tattoo inks with reference to the JRC report (Table 114 in the Background Document).

Soluble barium compounds

The hazard assessment of soluble barium compounds was based on barium chloride dihydrate, a readily soluble barium salt in water, for which toxicological data were available (a read-across approach).

The Dossier Submitter therefore based DNEL calculation on kidney effects of barium observed in NTP studies in rats and mice (NTP, 1994). The Dossier Submitter proposed a **DNEL of 0.60 mg Ba/kg bw/day** to be carried forward to the risk assessment of **soluble barium compounds**.

RAC agrees with this approach in general but considers that the PoD of 60 mg Ba/kg bw/day for renal effects of barium in rats should be corrected for percentage of oral uptake of barium chloride in rats (7%), which is markedly lower than the assumed 100% absorption after injection in the skin. Corrected PoD value is, therefore, approximately 4 mg Ba/kg bw/day, which leads to **DNEL of 0.04 mg Ba/kg bw/day**.

Insoluble barium compounds (i.e. barium sulphate)

The Dossier Submitter performed hazard and risk evaluation of insoluble barium salts by assessing information on barium sulphate ($BaSO_4$), as this is by far the most widely used

[34] Lakes are produced by precipitating dyes onto an insoluble base or stratum made by insoluble inorganic compounds, such as barium sulphate and aluminium hydroxide making them more stable to light and other chemicals (JRC 2015b).

insoluble barium salt. $BaSO_4$ is generally regarded as nontoxic due to its poor solubility, and is included in the List of colourants allowed in cosmetic products (CPR, Annex IV).

RAC agrees with the Dossier Submitter's proposal not to restrict $BaSO_4$ in tattoo inks at the present moment. RAC points out the need to investigate further the factors, both substance- and host-related, responsible for non-specific inflammatory and granulomatous reactions to tattoo inks.

Copper

Soluble copper

The CoE ResAP(2008)1, Table 3, recommends a maximum concentration of 25 ppm soluble copper (25 mg Cu/kg ink)[35] in tattoo inks. The reasoning behind the recommended limit value cannot be assessed since background papers are not available.

High concentrations of copper have been found in tattoo inks (up to 49,500 ppm according to JRC, 2015b report), but it is considered that this is most likely due to the use of green and blue pigments containing the copper ion (e.g. phthalocyanines). Although in the CoE ResAP(2008)1 only soluble copper is addressed, most of the analytical methods available today are not capable of distinguishing between the soluble form and copper incorporated in colourants.

The Dossier Submitter based their evaluation of copper on the DEPA (2012) report with the addition of supplementary information and chose to base a DNEL on the limit values for oral copper intake in populations with normal copper homeostasis, derived by the Scientific Committee on Food (SCF, 2003) and the World Health Organisation (WHO, 2004).

RAC agrees with the Dossier Submitter's proposal to derive a DNEL based on a tolerable daily intake (TDI) of 2.2 mg Cu/day, i.e. 0.037 mg Cu/kg bw/day, following WHO approach to provide an adequate margin of safety in populations with normal copper homeostasis. However, in line with Public Consultation comment (#1916) and corresponding Dossier Submitter's revision of the DNEL, RAC proposes to correct the derived DNEL value for 50% (based on lower oral absorption than assumed 100% after injection into the skin), obtaining **DNEL** value for intradermally applied copper of 1.1 mg Cu/day, or **0.019 mg Cu/kg bw/day**.

Insoluble copper - phthalocyanines used as colourants

Pigment Blue 15:3[36] and Pigment Green 7 are phthalocyanines and two essential colourants in tattoo inks.

[35] a definition of 'soluble' Cu in the context of tattoo inks is lacking

[36] Unsubstituted copper phthalocyanine blue exists in different crystal modifications. They are named with the Greek letters in the order of their discovery (alfa, beta, gamma, delta, etc) (PCI, 2018). The specific crystal modification decides the hue of the product. For example, alpha blue is a red shade copper phthalocyanine (Pigment Blue 15) and beta blue is a green shade blue (Pigment Blue 15:3). Alpha modification which is phase stabilised by partial chlorination is called solvent stable alpha blue or Pigment Blue 15:1, and alpha modification which is stabilised by partial chlorination to provide crystal stability and flocculation resistance is registered as Pigment Blue 15:2 (Kolor Jet Chemical, 2018).

The CoE ResAP(2008)1 recommends not to use phthalocyanine Pigment Green 7 (CAS no. 1328-53-6, CI 74260). It is listed in Annex II of the Cosmetic Product Regulation (entry #1369), which prohibits use in cosmetic products, when used as a substance in hair dye products, but it is allowed as a cosmetic colourant according to Annex IV (# 107) in other cosmetic products except eye products.

According to Annex II, entry No 1367 of the CPR, Pigment Blue 15 or Pigment Blue 15:1 ((29H,31H-Phthalocyaninato(2-)-N29,N30,N31,N32) copper) is not allowed in cosmetic products when used as a substance in hair dye products. However, it is allowed as a cosmetic colourant in cosmetic products in general according to the listing in Annex IV (entry #105). According to industry (JRC, 2015b), there is no suitable alternative to Pigment Blue 15, because the possible substitutes do not result in the same colour brilliance or they have greyish tones when blended with a white pigment.

Pigment Blue 17 and Direct Blue 86 are also copper phthalocyanine colourants used in tattoo inks. However, they are listed on Annex IV, column g (permitted use in rinse off only products) of the CPR and, therefore, in the scope of this restriction proposal.

In general, all the phthalocyanine complexes are of very low solubility in most solvents, including water, i.e. they do not dissociate to the phthalocyanine anion and copper ions to a considerable degree in aqueous solution. The various phthalocyanines are assumed to have similar toxicity profiles.

The limited available data would not trigger classification of phthalocyanines' for STOT RE, toxicity to reproduction, carcinogenicity or mutagenicity, and a derivation of a valid DNEL was judged not possible by the Dossier Submitter. Migration of phthalocyanine pigment particles to regional lymph nodes was described in humans (Schreiver et al., 2017), but the fate and bioavailability of intradermally injected and phagocytosed phthalocyanine pigment particles is inadequately explored. Phthalocyanine pigments particles, as described for Pigment Green 36 (Schreiver et al., 2017), are polydispersed in tattooed skin. Their size ranges from <50 nm to several micrometers, and they can be engulfed by phagocytes (Paul et al., 2013; Pang et al., 2017). In macrophages, phagocytosed particles are attacked by reactive oxygen species (ROS, hydroxyl radical and superoxide anion) and lysosomal hydrolytic enzymes (Zhao et al., 1991; Ward et al., 2006; Pang et al., 2017). It is not known whether ROS in mammalian cells can oxidise phagocytised phthalocyanines' pigment particles, and if they can, to what extent.

Copper phthalocyanine pigments are expected to be very resistant to degradation processes due to their extremely low solubility in water, large cross-sectional diameter, and (with the exception of the chlorine in chloro-substituted pigments) the lack of substituent groups associated with primary degradation (US EPA, 1994). They are considered to have excellent resistance to heat, light, acids and alkalis, and excellent lightfastness (Marzec, 2014), and the availability of copper ion from the copper phthalocyanine pigments by hydrolysis, photolysis, and aerobic and anaerobic transformations is considered negligible (US EPA, 1994). Phthalocyanines have extremely low solubility in water and organic solvents, but in aqueous solutions of strong oxidants the phthalocyanine ring is completely destroyed and

oxidised to phthalimide[37] (Loebbert 2000). However, chemical oxidation of phthalocyanines requires rigorous conditions, e.g. boiling in dilute nitric acid, treatment with ceric sulfate in dilute sulfuric acid, or by reaction with potassium permanganate (US EPA, 1994).

RAC considers that although physical-chemical properties of phthalocyanines do not indicate them being very bioavailable following intradermal injection, the uncertainties related to their hazard profile and fate once injected are too great to allow reliable risk assessment at the present moment.

RAC recommends further assessment of these colourants when more toxicological data become available.

Zinc

Zinc oxide (ZnO; CAS no 1314-13-2; Pigment white 4; CI no 77947) is insoluble in water and is one of four white colourants (all being inorganic pigments) reported to be used in tattoo inks. The presence of zinc (Zn; CAS no 7440-66-6) and zinc ferrite brown spinel (CAS no 68187-51-9; Pigment Yellow 119; CI no 77496) in tattoo inks has also been reported (JRC, 2015b).

Zinc is listed in Table 3 in the CoE ResAP(2008)1 as an impurity with maximum allowed concentration of 50 ppm (mg/kg) in tattoo inks. Zinc oxide is included in the list of colourants allowed in cosmetic products (Annex IV, entry no 144) of the cosmetics regulation (EC No 1223/2009). RAC supports the approach of the Dossier Submitter to adopt a NOAEL of 50 mg/day or 0.83 mg zinc/kg bw/day. This is based on the absence in humans of any adverse effects for a wide range of relevant indicators of copper-status as critical endpoint as indicated in the EFSA reports (EFSA, 2006, 2014) and supported by the SCCS opinion from 2017 (SCCS, 2017).

4. Substances with restriction on their use in cosmetic products (CPR) – qualitative evaluation

RAC, to assure consistency with other EU legislation, supports the Dossier Submitter's proposal that the following groups of substances can best be assessed in a qualitative manner in the context of this restriction as no further assessment is necessary because such was performed under the CPR, and paragraph 0.5 of Annex I of REACH applies:

[37] Phthalimide has no harmonised classification. It is of low acute and repeated dose toxicity, slightly irritating to the skin and eyes, and not sensitising or mutagenic (OECD SIDS 2005; Registration Dossier). Data on carcinogenicity are not available and, according to OECD SIDS (2005), there are some indications for reproductive toxicity at high doses, although the data are deficient (OECD SIDS 2005; Registration Dossier). Namely, in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) in rats, NOEL for reproductive and developmental toxicity was set to 250 mg/kg bw/day, based on pups' slightly reduced body weights during lactation period in 500 mg/kg bw/day group, and pups' death and body weight loss in one female dosed with 1000 mg/kg bw/day with abnormal histopathological findings (details not available). Phthalimide moiety is also contained by phthalidomide, a known human teratogen, but no evidence for embryonic/foetal lethality or teratogenicity was seen in oral study with phthalimide in hamsters and two oral studies in rabbits. However, the studies were described as limited due to an insufficient study design (low number of animals, only external malformations evaluated, only a single dose tested) (further data are not available) (OECD SIDS, 2005).

- substances on Annex II of the Cosmetics regulation (list of substances prohibited in cosmetic products);
- substances on Annex IV to CPR that are not allowed to be used in contact with mucous membranes, eyes or in prolonged contact with the skin (column "g") or subject to other conditions specified in columns "h" to "i" of the Annex (e.g., purity requirements).

The Dossier Submitter assumes that the intrinsic properties will manifest themselves to a higher degree when injected into the dermis in a tattoo than if applied on the surface of the body via cosmetic products. RAC agrees with this assumption, while pointing out the uncertainties already stated in the section *B.1.1.*above.

RAC also notes that by this approach, hazardous substances (e.g. skin sensitisers) without harmonised classification but included in Annex II or Annex IV of CPR will be in the scope of the restriction.

B.1.2.2. Information on emissions and exposures

B.1.2.2.1. Summary of proposal:

Tattoo ink is injected into the dermis where capillary action acts to draw the ink further into the dermis. This exposure route is unique to tattooing when compared to the scope of all other REACH risk assessments so far. For the purpose of (semi-)quantitative risk assessments, the Dossier Submitter estimates the exposure to substances in tattoo inks on the basis of a realistic worst case scenario, using the assumptions presented in Table 6.

Only one exposure scenario has been developed, consisting of isolated single tattoo sessions on 300 cm^2 skin. This is the typical maximum area of a full colour tattoo that can be made in one session (in one day), with the possibility of repetition until most of the body is covered. This exposure scenario will be protective for people getting both a single or several tattoos but also for whole body tattoos over a much longer timeframe.

Table 6. Parameters applied in the exposure calculation for tattoo inks

Parameter	Value
Size of tattoo per session (cm^2) - based on survey information from Danish tattooists (see below)	300
Pigmentation covering (%)	100
Weight of tattooed person (kg)	60
Amount of ink used per cm^2 (mg)	14.36
Amount of ink used per session (mg)	4 308
Bioavailability of pigments - Percentage of pigment having direct contact with inner tissues, including dermis Bioavailability of pigments - Percentage of pigment removed from tattoo area by body fluids	100% 100%
Bioavailability of impurities - Percentage of ink-fluids and soluble substances including impurities removed from the tattoo area	100%
Excretion of pigments	100%
Excretion for soluble substances incl. impurities	100%

B.1.2.2.2. RAC conclusion(s):

RAC agrees with the Dossier Submitter's approach to develop only one exposure scenario which represents a realistic worst case, assuming that a person repeatedly purchases the maximum size tattoo that is possible in one session (300 cm^2), until a full-coloured full-body tattoo is obtained (tattooing repeated once a month over approximately 5 years).

Taking into account the uncertainties described in the exposure assessment, RAC supports the justification for the input parameter values provided by the Dossier Submitter and presented in Table 4 (Parameters applied in the exposure calculation for tattoo inks). RAC also supports a value of 4 308 mg of ink used per session (for 300 cm^2 skin on which 14.36 mg ink/cm^2 is applied in one session), which is later used in the risk characterisation.[38]

B.1.2.2.3. Key elements underpinning the RAC conclusion(s):

Information on the toxicokinetics of chemicals contained in tattoo inks is very limited, leading to many uncertainties in the exposure estimate. Hence, RAC recognises that a number of conservative default estimates were of necessity used by the Dossier Submitter as listed below.

For the purpose of building the exposure scenario, the Dossier Submitter, chose a conservative approach to estimate bioavailability, assuming that there is:

- 100% bioavailability of injected tattoo inks (although bleeding that normally occurs at the tattoo site somewhat decreases this value), and
- 100% uptake of pigments, since human data showed that only a few percent of the initially injected pigment is required to keep the tattoo visible even after 20 – 30 years. Human and animal data have shown that tattoo pigments distribute in the body since

[38] See next section for explanation of assumptions.

they have been found in regional lymph nodes and in internal organs (e.g. liver).

The metabolism of tattoo colourants, especially azo colourants (which can produce PAA, some of them carcinogenic), was qualitatively considered by the Dossier Submitter, since it was not possible to assess the stability of the azo colourants quantitatively.

Especially regarding decomposition of azo pigments, the Dossier Submitter, also discussed some aspects of the removal of tattoos by laser treatment. Regarding distribution and excretion, a distinction was made between soluble and insoluble substances.

According to animal data, it seems that the amount of insoluble substances (i.e., pigments) at the injection site declines non-linearly, with a fast drop soon after the tattooing procedure. For example, animal data (Engel et al., 2010) showed approximately a 30% drop in the amount of azo pigment in the tattooed skin six weeks after the tattoo application. The authors of the study pointed out that "*a considerable amount of pigment should be transported away during the first weeks after tattooing because of the inflammatory reactions in the skin*". Human data indicates that only a small portion (few percent) of the originally injected pigment remains permanently at the tattoo site (Lehner et al., 2011). Due to the pigment's refractory properties and colour strength, this decrease in pigment content is not easily spotted by the human eye. The exact shape of the distribution curve is not known.

Although very limited information is available about the excretion of pigments, it is generally assumed that they are excreted to a low degree. Several mechanisms of tattoo fading have been proposed, including the dispersion of pigments through the skin, their phagocytosis and consequent removal, their metabolism in the skin, and the photochemical degradation of pigments (Cui et al., 2005). Therefore, it is considered that only a part of pigment which leaves the injection site becomes systemically available (and able to exert toxic effects away from the injection site).

Soluble substances (e.g., the liquid matrix in which the pigment is suspended, auxiliary substances, and some impurities) are considered to leave the injection site almost immediately, being distributed and excreted (via liver or kidneys) within hours or days. Nevertheless, solid ink particles, during their slow decomposition, may continue to release soluble substances (including impurities) leading to continuous exposure. Data on the kinetics of this process are lacking, and in the exposure assessment, the Dossier Submitter assumed that the impurities released from pigments are completely excreted before a new tattooing session, and that the sustained contribution from new release of impurities does not exceed the initial concentration of the impurities in the ink when injected into the body.

Exposure estimation

Based on an analysis of human and animal data and expert judgment, the Dossier Submitter developed one exposure scenario which consists of an isolated single tattoo session on 300 cm^2 skin repeated (approximately 60 times, i.e. once a month over approximately 5 years) until most of the body is covered. Namely, this scenario assumes that a person repeatedly gets the maximum size tattoo that is possible in one session, until a full-coloured full-body tattoo is obtained. Although most people are unlikely to get tattooed to this extent and exposures will generally be lower, nonetheless to be fully protective, it is justified by RAC to use the **maximum** value.

Based on the data from a recent (unpublished) Danish survey (Appendix F.1 Questionnaire on the tattoo process), a skin area with a 300 cm^2 full-colour tattoo obtained in one session (one day) was chosen as the typical maximum value. 73 tattoo artists responded with a completion rate of 60.3%, see Appendix F3 for further details. The reported average area was 588 cm^2 (median of 600 cm^2). When this value was corrected for full-colour tattoo (based on tattoo artists' responses, 300 cm^2 was obtained. RAC considers that this value is a realistic worst case scenario since it is based on direct information from the people performing the tattooing, and relies on a range of values (i.e., 38 responses).

The time interval between two tattooing sessions ranged between 1 and 15 months in the survey. In general, because of the healing process, at least 25 days are recommended by tattoo artists between tattoo sessions. The Dossier Submitter, therefore, chose this value while building the exposure scenario. RAC agrees with this value (as a realistic worst case) for the same reasons as stated above for tattooed skin area. RAC also considers that the value is physiologically justified (i.e., after a tattoo a scab/crust is created which falls of after approximately 1 week; the healing process continues and the skin appears healed after 4 to 6 weeks, although 6-12 months are required for full recovery).

Repeated tattooing

Limited data available in the published literature (Engel et al., 2008; Laux et al., 2016; Prior 2015) and a Danish EPA survey, show that the amount of ink deposited in skin during one tattoo session could vary greatly, by approximately two orders of magnitude (0.4 – 37.7 mg/cm^2). It is considered that an important factor influencing the quantity of ink deposited is the experience of the tattoo artist (an experienced tattooist is expected to use less ink). The Dossier Submitter chose Engel et al. (2008), since it is an experimental study (*in vitro* tattooing of human and pig skin) with the range of values (2.4 to 37.7 mg ink/cm^2)[39]. This is higher than in other reports (1.2 mg ink/cm^2 as the highest value found in experimental study of Prior, 2015; 1 mg ink/cm^2 reported in a review article prepared by Laux et al., 2016. The Dossier Submitter chose the 75th percentile of the range of values reported by Engel et al. (2008), thus obtaining 14.36 mg ink/cm^2. The 75th was chosen, instead of the 95th percentile normally applied in REACH consumer exposure assessment, since there is very limited data to assess the amount of pigment in the skin after tattooing. Therefore the data from the Engel study were considered as the worst case situation. According to ECHA Guidance "the use of the 75th percentile may be justified when the data set reflects worst case situation only". RAC agrees with this approach for the reasons presented by the Dossier Submitter.

To summarise, RAC considers that the assumptions for exposure estimation have been thoroughly studied and clearly presented by the Dossier Submitter together with the related uncertainties, and agrees with the input values chosen (Table 4. Parameters applied in the exposure calculation for tattoo inks), with a final value of **4 308 mg of ink used per session** (for 300 cm^2 skin on which 14.36 mg ink/cm^2 is applied in one session), for use in the risk characterisation.

[39] The Dossier Submitter considered a tattoo ink containing 25% pigment as a realistic composition, based on the typical range of pigment in tattoo inks (20-45%, according to JRC, 2015b; and for phthalocyanines 4.65-18.9% according to Danish EPA survey).

According to above mentioned Danish survey (Appendix F.1), repeated tattooing (such as once a month through a year) is common. Taking this into account , as well as the continuous release of impurities from some of the pigments and the lack of knowledge on the toxicokinetics of the colourants in the body, RAC agrees with the Dossier Submitter to compare the value of 4 308 mg of ink used per session with a DN(M)EL related to lifetime exposure. Namely, this scenario assumes that a person is exposed to chemicals present in the tattoo ink, every day throughout their lifetime.

This scenario is based on a considerable simplification of tattoo ink toxicokinetics, which is inevitable due to the lack of crucial data on the chemicals applied via tattooing, especially on the temporal pattern of distribution and excretion. RAC is, nevertheless, of the opinion that the scenario is robust enough to estimate exposure to soluble substances which are not expected to accumulate in the organism and are excreted relatively quickly from the organism (within a few weeks). In fact, it is expected to overestimate exposure due to continuous excretion of substances between two sessions, especially once tattooing completely stops (e.g. after obtaining full-body tattoo after 5 years of tattooing).

Azo pigments in tattooed skin, although considered insoluble, do release PAAs over time. PAAs, nevertheless, are rapidly metabolised and excreted from the body, so accumulation is not expected. For example, according to the POISINDEX(R) MANAGEMENTS database, aniline rapidly metabolises to p-aminophenol (also after percutaneous absorption), and almost 90% of this metabolite is eliminated in the urine within 24 hours after exposure. Similarly, in rats about 72% of intraperitoneally given dose was excreted in urine after 72 hours (Sapota et al., 2003).

If the excretion of soluble substances in tattoo ink is not so fast, however, this scenario could, theoretically, underestimate exposure. Lead, barium, copper and zinc are examples of such substances, for which (semi-)quantitative risk assessment has been performed. This is further discussed in the section B.1.2.4. *Uncertainties in the risk characterisation*.

B.1.2.3. Characterisation of risk(s)

B.1.2.3.1. Summary of proposal:

Quantitative risk assessments and derivation of DNELs were made for a number of threshold substances, such as those toxic to reproduction and selected impurities. Some impurities and non-threshold substances were risk assessed in a semi-quantitative way with derivation of DMELs, primarily for the derivation of concentration limits but also for risk characterisation.

For the purpose of the risk characterisation of substances with (semi-)quantitative assessment, the exposure is compared with a DN(M)EL related to lifetime exposure as per ECHA CSA Guidance R15. Table 13 and 14 in the Background Document describe the results of this comparison. The Dossier Submitter proposes that the following substances are restricted in tattoo inks based on this (semi-)quantitative assessment: PAAs, reproductive toxins categories 1 and 2; methanol; arsenic; barium; copper and zinc.

The remaining substances in the scope were assessed by a qualitative approach: substances classified with regard to skin irritant/corrosion, eye damage/ irritatant, sensitisation, mutagenicity and carcinogenicity; lead compounds due to their non-threshold effects

(although a concentration limit was set using the DMEL); substances on the CPR as described in the scope and the remaining substances on Tables 2 and 3 in the CoE ResAP(2008)1.

Concentration limits

Two different restriction options (RO1 and RO2) are included in this restriction proposal, which differ mainly in terms of the concentration limits proposed, with RO1 having stricter limits for some substances than RO2 (for more detailed information see 2.2 and Annex D). The restriction options and concentration limits are presented in Table 11 in the Background Document).

For the substances assessed in a (semi-)quantitative manner, DN(M)ELs were derived and compared to the exposure assessment in the exposure scenario. To identify the concentration limit, the content of the hazardous substance corresponding to a Risk Characterisation Ratio (RCR) < 1 or an excess lifetime risk < 10^{-6} was calculated. For lead, the concentration limit was based on 0.1% extra risk of developmental neurotoxicity at 0.05 µg Pb/kg bw per day ($BMDL_{01}$/10).

B.1.2.3.2. RAC conclusion(s):

RAC agrees that the qualitative risk characterisation and assessment is an acceptable and practical solution for substances for which non-threshold effects were agreed. This takes into account that a reference dose-response after intradermal injection, which could be used for characterising the potency of a substance, will not be available for any substance considered, since intradermal exposure is not foreseen for studies required for registration purposes. In addition, any determination of a systemic dose of the substances injected intradermally for making a permanent coloration of the skin would be made with high level of uncertainty.

The quantitative or semi-quantitative risk characterisation approach for the other substances, for which derivation of DNEL or DMEL was possible is appropriate and can be used for risk assessment.

The concentration limits proposed by the Dossier Submitter and originating from various sources, such as CPR, CLP, CoE ResAP and those derived specifically for this restriction proposal, are in general supported by RAC. In certain cases, RAC suggests some deviations from concentration limits proposed under RO1 and RO2 (Table S2), i.e. for skin sensitisers, skin corrosives or irritants or serious eye damaging or irritant substances, and reprotoxic substances.

B.1.2.3.3. Key elements underpinning the RAC conclusion(s):

Available human case studies show that specific adverse health effects occur in the tattooed human population, from mild reactions such as discomfort, mild swelling and erythema to deep ulcerative lesions with disfiguring scarring. Tattoo reactions have been reported for almost every ink colour (the Background Document, section D.6.1. *Human health impacts*). However, while the link is rather firm for local non-neoplastic effects (although exact the pathophysiological mechanism has often not been determined), the relationship to skin tumours and systemic effects, such as malignant tumours in internal organs, systemic immunological responses or reprotoxic effects, is much less clear. An exception for systemic effects is the general eczema observed sometimes in tattooed persons (e.g. caused by nickel

salts as industrial contamination in tattoo inks).

The prevalence and incidence of adverse health effects is difficult to assess, even for localised (skin) reactions, for many reasons. There are no central registries of tattoo-related health effects, and epidemiological population-based studies with adequate random sampling designs are not available. Also, there are no longitudinal studies which could provide information on the incidence of tattoo-related adverse health effects. Only few patients consult their physician regarding minor cases, consulting instead their tattooist (Serup et al., 2015a; Kluger, 2012; Klügl et al., 2010). The diagnostic procedures are rarely performed and even when done they are not always considered reliable (e.g. patch test for diagnosing contact sensitisation; please see paragraph below on skin sensitisation).

Additionally, as the onset of adverse tattoo reactions (e.g. allergic) can occur from weeks to decades after tattooing, contemporary statistical data probably does not reflect the advancements in tattooing practices and inks. Namely, as described in the Background Document, although the composition of black ink has not changed much over the last several decades (primarily soot derivatives and carbons, including polycyclic aromatic hydrocarbon impurities), the composition of coloured inks has changed since the 1970s, in a way that toxic metals (e.g. mercury, cadmium, chromium, cobalt and lead) have been replaced with synthetic organic pigments, such as azo dyes and polycyclic compounds, including phthalocyanines.

The risk of malignant, systemic and reproductive effects related to tattoo inks is especially infeasible to assess in the human population. Cancer is a multi-aetiological disease, usually requiring decades to become clinically observable, and a casual links with specific chemicals in tattoo ink are difficult to establish. Regarding reprotoxic effects, additional health risks for the mother or the baby due to the mother acquiring a tattoo have not been so far studied systematically. Nevertheless, exposure to reprotoxic substances in tattoo inks is evident (JRC, 2015b), and, although it is difficult to assess the risk of reproductive toxicity, concern remains and RAC considers that precautionary action is required.

In conclusion, RAC agrees with the Dossier Submitter that chemicals in tattoo inks undoubtedly pose a health risk for the human population, although incidence and prevalence of tattoo-related adverse health effects is difficult to assess at the present moment.

RAC considers that there is enough evidence to demonstrate the risk of local (skin) effects, including both allergic and non-allergic non-infectious inflammatory reactions, while the evidence for systemic (except for general eczema) or malignant effects is much less clear. This especially applies to carcinogenic and reprotoxic effects, which, even if present, are not expected to be easily detected in the tattooed population. Nevertheless, RAC is of the opinion that the risk of carcinogenic, reprotoxic and other systemic effects cannot be excluded. This conclusion takes into account the intrinsic properties of chemicals that are or could be found in tattoo inks in the future, and toxicokinetic data from humans and animals which indicate that only a few percent of the injected tattoo ink is retained in the tattooed skin, while the rest is potentially systemically available, over several days to several decades.

RAC also generally agrees with the Dossier Submitter's approach to risk characterisation, but, in certain cases, suggests some deviations from the concentration limits proposed under RO1 and RO2.

Qualitative approach

For substances where it is difficult to identify a reliable dose-descriptor, the health risk was evaluated in a qualitative manner (carcinogens, mutagens, lead compounds, skin sensitisers, skin and eye irritant or corrosive substances). The exposure assessment indicates that significant exposure can occur due to the delivery of tattoo inks into the dermis and since these are non-threshold substances it cannot be excluded that risks to consumers can occur. It is agreed that there is no single, standardised methodology for performing a qualitative assessment. In addition, there are no relevant operational conditions (OC) and risk management measures (RMM) for the intradermal injection of tattoo inks.

Therefore, RAC agrees with the Dossier Submitter proposal that the substances should be restricted in tattoo inks based on the risk from exposure to substances classified with regard to skin irritant/corrosion, eye damage/ irritant, sensitisation, mutagenicity and carcinogenicity.

Derivation of concentration limits[40]

The concentration limits supported by RAC are set out in Table 7 (i.e., RAC modified RO1).

Table 7. Concentration limits proposed by the Dossier Submitter and RAC

Substance group	DS Concentration limits (% w/w)		RAC modified RO1 Concentration limits (% w/w)			
	RO 1	RO 2	Risk-based proposal	Practical approach	Justification for practical CL	Reason for deviation from Dossier Submitter's proposal
CPR Annex II	Shall not contain	0.1	Should not contain	0.00005	as for Carc/Muta	RO 1 not enforceable and RO2 too high for CMs (substances with lowest CL in Annex II).
CLP Carcinogenic 1a/b	Shall not contain	CLP GCL (or SCL)	Should not contain	0.00005	same approach as PAHs	RO 1 not enforceable and RO2 CL not appropriate as not risk based.
CLP Carcinogenic 2	Shall not contain	CLP GCL (or SCL)	Should not contain	0.00005	same approach as PAHs	RO 1 not enforceable and RO2 CL not appropriate as not risk based.
CLP Mutagenic 1/ab	Shall not contain	CLP GCL (or SCL)	Should not contain	0.00005	same approach as PAHs	RO 1 not enforceable and RO2 CL not appropriate as not risk based.
CLP Mutagenic 2	Shall not contain	CLP GCL (or SCL)	Should not contain	0.00005	same approach as PAHs	RO 1 not enforceable and RO2 CL not appropriate as not risk based.
CLP Reprotoxic 1a/b	0.0014	CLP GCL (or SCL)	Should not contain	0.001	based on data for DBP and an overall assessment of the reprotoxic substances	PoD for RO1 reassessed and RO2 CL not appropriate
CLP Reprotoxic 2	0.014	CLP GCL (or SCL)	Should not contain	0.001	as above	PoD for RO1 reassessed and RO2 CL not appropriate
CPR Annex IV (column g)	Shall not contain	0.1	Should not contain	0.00005	as for Carc/Muta	RO1 not enforceable and RO2 too high for CMs (substances with lowest CL in Annex II).
CPR Annex IV (column h-i)	CPR, Annex IV limits	CPR, Annex IV limits	CPR, Annex IV limits	CPR, Annex IV limits		As per CPR assessment
PAH with harmonised	0.00005	0.00005	Should not	0.00005	as per CL for toys in Annex	Lower CL is proposed for BaP,

[40] See Appendix 4 to this opinion for further details

Substance group	DS Concentration limits (% w/w)		RAC modified RO1 Concentration limits (% w/w)			
	RO 1	RO 2	Risk-based proposal	Practical approach	Justification for practical CL	Reason for deviation from Dossier Submitter's proposal
classifications as CM			contain	BaP: 0.0000005% (5 ppb)	XVII, entry #50 BaP: as in Table 3 of CoE ResAP(2008)1	as in CoE ResAP(2008)1, due to its higher carcinogenic potential compared to other PAHs
PAAs of concern (dissolved fraction)	0.00003 0.0005#	0.00003 0.0005#	Should not contain	0.00006 0.0005	0.00006% based on DMEL for carcinogenicity; 0.0005% due to recognised practical reasons for higher limit (technical achievability)	No deviation from practical CL of 0.0005% proposed by the Dossier Submitter, which is stated in Table A in the restriction proposal
Azo dyes with relevant classification (CMR, SS), or which could decompose to PAAs of concern	0.1	0.1	Should not contain	0.1	practical limit to discourage use, as intentionally used pigments are normally used in higher concentrations	-
CLP Skin sensitisers 1a	0.1	0.01	Should not contain	0.001	95 percentile level of protection for strong SSs	RO1 too high to prevent risk and RO2 CL not appropriate.
CLP Skin sensitisers 1, 1b	0.1	0.1	Should not contain	0.001	95 percentile level of protection for strong SSs	RO1 too high to prevent risk and RO2 CL not appropriate
CLP Skin irritant & corrosive 1or 1a/b/c, 2	0.1	CLP GCL (or SCL)	Should not contain	0.01	based on human and animal data showing 10 to 100 times higher irritant potency of intradermal compared to topical application	RO1 too high to prevent risk and RO2 CL not appropriate
CLP Eye irritant & damaging 1, 2	0.1	CLP GCL (or SCL)	Should not contain	0.01	same as above	RO1 too high to prevent risk and RO2 CL not appropriate
Methanol	10.9	10.9	11	11	based on OEL & realistic worst case exposure scenario	-
Impurities in ResAP(2008)1 Table 3 Cadmium	0.00002	0.00002	Should not contain due to its CMR hazards	0.00005	as for Carc/Muta	Group approach (as for other CM) to make the restriction simpler
Chromium(VI)	0.00002	0.00002	Should not contain due to its CMR and SS hazards	0.00005	as for Carc/Muta	Group approach (as for other CM) to make the restriction simpler
Mercury	0.00002	0.00002	Should not contain due to its	0.00005	as for substances on Annex II of the CPR	Group approach (as for other Annex II CPR substances) to

Substance group	DS Concentration limits (% w/w)		RAC modified RO1 Concentration limits (% w/w)			
	RO 1	RO 2	Risk-based proposal	Practical approach	Justification for practical CL	Reason for deviation from Dossier Submitter's proposal
			R hazards and Annex II of CPR			make the restriction simpler
Copper*	0.025	0.025	0.025	0.025	quantitative derivation of CL with correction for 50% oral absorption	DS revised DNEL based on PC comments
Zinc*	0.23	0.23	0.2	0.2	based on DNEL for humans	-
Barium*	0.84	0.84	0.056	0.05	based on rodents' DNEL for nephrotoxicity of $BaCl_2$, corrected for 7% oral absorption in rats	Revised DNEL calculated
Nickel	0.001	0.001	Should not contain due to its SS hazards	0.0005	technically achievable limit	RO1 & RO2 too high to prevent risk
Selenium	0.0002	0.0002	Should not contain[1]	0.0002	as in CoE ResAP(2008)1, as a proxy for technically achievable limit	-
Antimony	0.0002	0.0002	Should not contain[1]	0.00005	as for substances on Annex II of the CPR	Group approach (as for other Annex II CPR substances)
Lead	0.00007	0.00007	Should not contain	0.00007	quantitative derivation of CL	-
Cobalt	0.0025	0.0025	Should not contain due to its C, R, SS hazards[2]	0.00005	as for Carc/Muta	RO1 & RO2 too high to prevent risk - group approach (as for other CM)
Arsenic	0.00000082	0.00000082	Should not contain[1]	0.00005	as for other Carc	Dossier Submitter limit not practical as would prevent use of many pigments - group approach (as for other CM)
Organometallic tin	0.005[4]	0.005	Should not contain due to CMR and SS hazards[3]	0.00005	as for Carc/Muta	Group approach (as for other CM)

[#] A CL of 0.00005 % is proposed by the Dossier Submitter due to socio-economic reasons; * Soluble

[1] CPR, Annex II; [2] RAC opinion on cobalt (CLH-O-0000001412-86-172/F), proposing its harmonised classification also as Carc. 1B, Muta. 2 and Repr. 1B, has been adopted in September 2017; [3] E.g. dibutyltin hydrogen borate (Muta. 2, Repr. 1B, Skin Sens. 1), triphenyltin acetate or hydroxide (Carc. 2, Repr. 2), or tributyltin compounds (Repr. 1B); [4] Original proposal by

Dossier Submitter for tin with CL= 0.005% w/w as in CoE ResAP(2008)1.
SS – skin sensitiser; CMR – carcinogenic/mutagenic/reprotoxic; Carc – carcinogenic; R – reprotoxic

B.1.2.4. Uncertainties in the risk characterisation

RAC agrees with the main sources of uncertainties and their impact on the conclusions, RCRs and concentration limits, as described in the Background Document by the Dossier Submitter.

Exposure scenario

In addition to the uncertainties listed in the background document, RAC identifies another uncertainty related to the exposure scenario. As pointed out previously, if excretion of soluble substances in tattoo ink is not so fast, the exposure scenario developed by the Dossier Submitter could, theoretically, underestimate exposure. Lead, barium, copper and zinc are examples of such substances.

The elimination half-life of barium in human bone tissue is 50 days, although it seems that only small portion of soluble barium in blood reaches the bone (e.g. in one subject after an intravenous injection of ^{133}Ba, 84% of the radiolabelled barium was excreted within the first 6 days; ATSDR Barium), and, in addition, Ba^{2+} does not accumulate in the bone with age.

The elimination of copper occurs slowly, with the biological half-life of dietary copper reported to be up to 33 days (POISINDEX(R) MANAGEMENTS database), and half-lives of months and years in internal organs, such as heart and brain (ATSDR Copper, 2004). However, copper is an essential element with homeostatic regulation in the human body (physiological levels of copper in the body are held constant by alterations in the rate and amount of copper absorption, compartmental distribution, and excretion; ATSDR Copper, 2004), and the risk assessment was based on a tolerable daily intake, including population of children. Underestimation of risk, is therefore, not expected.

It is stated in the Background Document that the kinetics of zinc absorption and elimination follow a two-component model: initial rapid phase with a half-life in humans of 12.5 days and the slower phase with a half-life of approximately 300 days. However, taking into account the low zinc concentration found in tattoo inks and the homeostatic mechanism present in the body, it is not expected that the risk from zinc in tattoo inks would be underestimated.

In adult humans, the half-life of lead in blood and soft tissues is 20–30 days, 2–8 years in trabecular bone and more than 20 years in cortical bone, and it is well-known that lead accumulates in bone tissue during lifetime. The Dossier Submitter based risk assessment for lead on the RAC opinion on lead and lead compounds in jewellery, which was based on EFSA's CONTAM Panel assessment, with a modification. In the EFSA's assessment, the relationship between dietary lead intake and blood lead levels in children was estimated using the Integrated Exposure Uptake Biokinetic (IEUBK) model. Comparing lead absorption from a meal to lead being released from tattooed site during several weeks and years following tattooing session, it could be speculated that this model (which models movement of lead between internal compartments and to the excretion pathways, and, combined with the total lead uptake, continuously recalculates the amount of lead in each body compartment, including changing concentration of lead in blood) cannot accurately predict lead exposure following tattoo injection. RAC is aware, nevertheless, that it is not

feasible to build more accurate exposure model, due to lack of data on both tattoo inks toxicokinetics and lead toxicokinetics following tattooing.

Hazard and risk assessment

The main uncertainty is a general lack of data for risk assessment of intradermally applied chemicals. As the Dossier Submitter pointed out, "a degree of uncertainty lies in the fact that no risk assessment of the respective substances has been performed for the application "injection under the skin". It is possible that for tattooing, a lower maximum concentration needs to be allocated to certain substances. In order to alleviate this uncertainty RAC took into account difference in exposure route whenever possible (e.g. by correction for oral absorption factor or comparing toxicity data for intradermal vs. topical route for skin and eye irritants). Nevertheless, in number of situation data were insufficient to adequately address this issue.

Other uncertainties include:

- Epidemiological data have too many limitations to provide a reliable estimate of incidence of tattoo-related adverse effects (discussed in more details in section B.1.2.3.3 and Appendix IV – Skin sensitisation).
- A clear causal link between adverse effect and specific chemical(s) in tattoo ink is possible to establish, but in limited number of cases (e.g., some azo pigments and quinacridones, some metals; Gaudron et al., 2015; CHDP, 2015; Tammaro et al., 2011, 2015), since in many cases tattoo ink composition is unknown, metabolism in the skin and degradation products (due to e.g. laser treatment or sun exposure) are not well researched, or diagnostic procedure has not been performed.
- There is a lack of data allowing for risk assessment of chemicals and their degradation products during laser removal. This issue the Dossier Submitter has not addressed in detail, although laser decomposition of azo colourants has been taken into account.
- There are some adverse non-infectious reactions in humans for which:
  - it is not expected to be observed in regular toxicological testing, such as papulo-nodular reactions, since the intradermal route is not tested in regular toxicological studies, or sun-related adverse reactions of tattooed skin[41] (Hutton Carlsen and Serup, 2014), and for which a pathophysiological mechanism is not fully elucidated;
  - a link to specific substance(s) in ink is missing but it is suspected that the chemical composition of the ink is a factor;
  - other factors (e.g. tattooing technique) may also be responsible (e.g. pigment overload).
- For potential alternatives for which health risks are unknown, the risk reduction capacity cannot be assessed.

[41] This refers primarily to standard toxicological testing in frame of the CLP. Cosmetic product safety information, however, should contain data on photo-induced toxicity in the case of UV absorption (paragraph 8, part A of the CPR).

The unknown health risks of colourants injected in the form of nanoparticles (NP) pose another uncertainty. It has been shown that, except for the white colourants, many tattoo inks of various colours present on the market contained significant amounts of NP, with the black colourants being almost completely NP (Høgsberg et al., 2011). Also, colourants can degrade to NP, as observed following laser treatment (JRC, 2015b). In a recent study by EcoMole Ltd. and the VŠB Technical University of Ostrava (Hynes et al., 2018), commissioned by the European Union Observatory for Nanomaterials (EUON), it was pointed out that adverse effects of a NP material cannot always be derived from the known toxicity of the macro-sized material of the same chemical composition. Namely, in contrast to conventional chemicals, where chemical composition principally determines toxicokinetics and toxic properties, nanomaterial toxicity depends on various physical and chemical properties, such as the size, shape, crystalline structure, surface electric charge, chemical compositions of the core and shell (surface coating) and purity. While NP-colourants could be involved in various adverse effects of tattooing, such as foreign body reactions and adverse photochemical reactions, the knowledge gaps are too big to allow hazard and risk assessment of NP in pigments at the present moment (Hynes et al., 2018). Ongoing research in the field of nanomaterial toxicity, together with EU actions such as EUON which provides information about existing nanomaterials on the EU market (e.g., list of nano-pigments on the EU market), as well as about the safety, innovation, research and uses of nanomaterials, are expected to reduce these knowledge gaps in the future.

Azo colourants and PAAs

Types of PAAs found in tattoo inks are expected to be influenced by the type of azo colourants present on the market, since azo colourant molecular structure determines decomposition mechanisms (e.g. amide azo colourant *vs.* azo colourant that do not contain amide functional group). The EU market survey reports (e.g. JRC, 2015b) state the types of azo colourants present on the market, but without quantitative data on usage (amount or frequency). For example, in analysed tattoo inks samples, lower percentage of PAAs formed only by azo bond cleavage could be, hypothetically, consequence of lower usage of azo pigments which cannot decompose via amide hydrolysis. Further, as stated in the Background Document, 50% of the observed PAAs cannot be explained by either azo cleavage or amide hydrolysis, indicating that other decomposition mechanism(s) may be involved, and/or that there could be other azo colourants in use than those 67 identified in the Joint Research Centre study (JRC, 2015b). This uncertainty could lead to **underestimation of the risk** if different types of azo colourants will be used in the future, compared to present situation. However, the uncertainty is alleviated by the proposal to restrict azo colourants based on 3,3'-dichlorobenzidine (by photo-decomposition criteria), a carcinogenic PAA that was the most frequently found PAA expected to be formed only by azo bond cleavage (Table 33 in the Background Document). Also, 16 azo colourants in table 2 of the CoE ResAP(2008)1, proposed to be included in the scope of this restriction, do not decompose via amide hydrolysis. PAAs of concern are supposed to originate from these colourants either from cleavage of azo bond or from colourant's production (DEPA, 2017c).

Present analysis of tattoo inks on the EU market can take into account only PAAs formed in tattoo inks before their application into the skin, although skin and systemic metabolism

of azo colourants may qualitatively and quantitatively differ from degradation processes present in tattoo inks before the use (e.g. by bacterial degradation). Xenobiotic metabolism in human skin is not yet adequately explored (Oesch et al., 2014), especially regarding dermis (compared to epidermis), although metabolic differences between these two skin layers have been recognised (Oesch et al., 2014; Zappa et al., 2014; Wiegand et al., 2014). In general, it is considered that dermis has lower metabolic activity compared to epidermis and liver, including phase I metabolism enzymes (which includes reactions of amide hydrolysis and azo bond cleavage) (Zappa et al., 2014; Wiegand et al., 2014, Serup, 2013). This uncertainty could lead to **overestimation of the risk**.

Arsenic

There is an uncertainty linked to linear simplification of dose-response curve for arsenic carcinogenicity (based on WHO/FAO risk assessment built on lung and urinary bladder cancer data from prospective study in population exposed to arsenic in drinking water in north-eastern Taiwan), since, as pointed out in RAC opinion (ECHA, 2013), the mechanistic evidence is suggestive of non-linearity and the excess risks in the low exposure range might be an overestimate. Nevertheless, reliable data for carcinogenic effects of arsenic at lower doses are not available. This uncertainty is expected to lead to overestimation of the risk.

Another uncertainty is unknown pattern of inorganic and organic arsenic species and compounds found in groundwater compared to those present in tattoo inks. Since, as stated in the Background Document, most arsenic compounds are soluble in water, this uncertainty is not expected to greatly influence arsenic bioavailability in groundwater compared to tattoo inks. On the other hand, differences in proportion of arsenic species could lead to differences in toxic effects (due to different level of toxicity between e.g. trivalent and pentavalent inorganic arsenic species). Nevertheless, since pattern of arsenic species spatially and temporally varies in groundwater (Qin et al., 2014), and due to inadequate data on arsenic speciation both in groundwater and tattoo inks, this uncertainty cannot be alleviated at the present moment and could lead both to **underestimation** and **overestimation of the risk**.

B.1.3. Evidence if the risk management measures and operational conditions implemented and recommended by the manufactures and/or importers are not sufficient to control the risk

B.1.3.1. Summary of proposal:

There are no relevant risk management measures and operational conditions that can be applied to the intra dermal injection of tattoo inks.

B.1.3.2. RAC conclusion(s):

RAC agrees with the Dossier Submitter that there are no relevant risk management measures and operational conditions that can be applied to intentional intradermal application of a tattoo ink of essentially unknown composition.

B.1.3.3. Key elements underpinning the RAC conclusion(s):

As pointed out it the Background Document, traditional operational conditions (OCs) and risk managements measures (RMMs), such as level of containment and use of personal protective equipment, do not have relevance to the intradermal injection of tattoo inks, and the only way to manage the risk related to tattooing is to limit the content of potentially hazardous substances in the inks.

B.1.4. Evidence if the existing regulatory risk management instruments are not sufficient

B.1.4.1. Summary of proposal:

Currently, there is no EU-wide measure specifically for tattoo inks or PMU although several pieces of horizontal legislation apply to tattoo inks. The General Product Safety Directive (Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety) applies, however, the GPSD is not widely used for tattoo inks and PMU in the EU. Seven EU Member States have translated the CoE ResAP into national law. The Cosmetics Products Regulation (CPR) (Regulation (EC) 1223/2009) defines cosmetic products as "any substance or mixture intended to be placed in contact with the external parts of the human body ….." As tattoo inks and PMU are injected into the dermis, they do not fall into the scope of the CPR. The EU Biocides Regulation (BPR) 528/2012 covers a very diverse group of products, including preservatives. As tattoo inks are not considered cosmetics, the in-can preservative used in tattoo inks are not subject to the cosmetics regulation, and therefore are de facto subject to the BPR rules. As the BPR regulates only preservatives as part of the tattoo ink mixture, the use of pigments, additives and fillers in tattoo inks is not in its scope. The CLP requires assignment of hazard categories, based on available information, to substances and subsequent labelling provisions to indicate the intrinsic hazard of the substance to the users. These requirements already apply to tattoo inks and do not in themselves restrict the placing on the market of mixtures containing these substances.

Therefore, the Dossier Submitter outlines in their proposal that the only way to manage the risk in the case of receiving tattoos is to limit the presence of unwanted substances in tattoo inks. No other risk management measures are appropriate and a total ban is not realistic, as this would ban tattooing as such. Therefore, the Dossier Submitter proposes to manage the risk by setting concentration limits for the chemical substances in tattoo ink. These concentration limits are derived on the basis of (semi-)quantitative and qualitative risk assessments using realistic worst case exposure assumptions. When the content of the substances in tattoo and PMU ink is limited to the proposed concentration limits, the risk from exposure described in the exposure scenario for tattoos is considered to be adequately controlled for threshold substances with a quantitative approach. For non-threshold substances, such as PAAs with carcinogenic and mutagenic effects, a cancer risk level of 10^{-6} could be seen as indicative tolerable risk level for the general population and has been used by the Dossier Submitter with derivation of DMELs for the purposes of deriving concentration limits.

For the remaining substances (i.e., substances with harmonised classification or those

included on the basis of assessments under other legislation (national or ResAP)), it is expected that the introduction of a limit that discourages their intentional use (i.e., a practical limit) and minimises their presence in tattoo ink mixture (i.e., by introducing limits consistent with assessment other legislation) would lead to minimising the probability that exposure to a hazardous substance will result in an adverse effect (e.g., the incidence of skin sensitisation observed and reported after receiving a tattoo).

While measures to limit the concentration of hazardous substances in tattoo inks are in place in seven Member States, the majority of EU Member States do not have such provisions.

B.1.4.2. RAC conclusion(s):

RAC agrees with the Dossier Submitter that there is no EU-wide measure that applies specifically for tattoo inks only national measures in some Member States and that other EU-wide regulatory risk management instruments are not sufficient.

B.1.4.3. Key elements underpinning the RAC conclusion(s):

RAC considers that the Dossier Submitter appropriately justified that national and EU wide legislation not specially focused to tattooing, such as the General Product Safety Directive, the Cosmetics Products Regulation, the CLP Directive, the EU Biocides Regulation, the EU Ecolabel Regulation, separate legislation on tattoo inks and other voluntary actions, cannot adequately decrease health risks related to chemicals present in tattoo inks, due to limited scope, practicality issues, inadequate effectiveness, or lack of consistency and harmonisation across the EU. Some specific considerations are:

- CoE ResAP(2008)1 (and its predecessor CoE ResAP(2003)2), is an advisory, non-binding measure specific for tattoo inks, and it has been introduced into national legislation in approximately one-third of EEA Member States. On the other hand, tattoo-related adverse health effects and use of tattoo inks containing hazardous substances, such as carcinogenic or skin sensitising substances, have been recorded throughout the EU, including Member States with CoE ResAP incorporated into national legislation (JRC, 2016a; JRC, 2015b; DEPA, 2012), showing rather high level of non-compliance (please also see SEAC section B.2.3.). All these facts indicate a need for a binding EU-wide legal measure. Also, the risk assessment of substances that can be present in tattoo inks showed that not all of them have been covered by CoE ResAP(2008)1, i.e. skin sensitisation, corrosion, or irritant and eye damage or irritant.
- Under the provisions of the General Product Safety Directive (GPSD), manufacturers are required to supply safe products. However, as a result of the increased popularity of tattoos and reported adverse effects, national legislation was introduced to address the risk in selected Member States. This indicates that the provisions in the GPSD are too general to ensure adequate control of the chemical risks to human health EU-wide.
- The scope of the Cosmetics Products Regulation (CPR) does not cover intradermal injection and therefore tattoo inks are excluded from its scope.

- The EU Biocides Regulation (BPR) regulates only the preservatives part of the tattoo ink mixture.
- The CLP labelling requirements do not in themselves restrict the placing on the market of mixtures containing these substances.
- The EU Ecolabel Regulation currently does not apply to tattoo inks. Also, it is a voluntary measure, not binding and could not restrict hazardous substances in tattoo inks in a consistent and harmonised manner.
- Effectiveness of voluntary measures by industry (such as provision of information by tattoo artists on the risks and after care; an exchange of information through the supply chain on tattoo inks), largely depends on the level of organisation of the sector, which varies substantially across the EU. Therefore, they are not expected to restrict hazardous substances in tattoo inks in an effective and harmonised manner.
- Separate (stand-alone) legislation on tattoo inks could be considered as an effective type of legislation, since it would also regulate other issues related to safety of tattooing procedure (e.g. hygiene, registration, certification or training requirements of tattoo artists), and would be focused on intradermal route of application of chemicals. RAC agrees, however, that it will be difficult and time consuming to negotiate EU-wide stand-alone legislation, regarding a number of issues (such as business licenses, training and certification) that are currently within the jurisdiction of local and regional authorities.

B.2. JUSTIFICATION IF ACTION IS REQUIRED ON AN UNION WIDE BASIS

Justification for the opinion of SEAC and RAC

B.2.1. Summary of proposal:

The Dossier Submitter concluded that, although no fully quantitative analysis of the risks of all substances that are currently used in tattoo inks is possible, the qualitative and quantitative assessment has demonstrated that risks to human health are not adequately controlled. Therefore, the risks associated with EU manufactured or imported tattoo inks need to be addressed on a Union-wide basis for two reasons:

a) a harmonised high level of protection of human health and the environment, and

b) the free movement of goods within the Union.

B.2.2. SEAC and RAC conclusion(s):

Based on the key principles of ensuring a consistent level of protection across the Union and of maintaining the free movement of goods within the Union, SEAC and RAC support the view that any necessary action to address risks associated with hazardous substances in tattoo inks should be implemented in all Member States. Tattoo inks are marketed and used throughout the EU. Therefore, action is required and it should be taken on a Union wide basis.

B.2.3. Key elements underpinning the SEAC and RAC conclusion(s):

RAC

Tattoo and PMU procedures have an increasing trend worldwide, including Europe. Tattoo practice and a risk for adverse health effects related to exposure to hazardous chemicals in tattoo inks exists in all Member States, including those with tattoo-specific national legislation (as shown in recent reports, e.g. JRC, 2016a), due to variable compliance rate with national legislation and trans-boundary trade between Member States.

EU wide measure is expected to harmonise level of protection across the EU, and to decrease non-compliance to tattoo-specific national legislation in EU countries in which such legislation is implemented. In addition, most of the inks are imported and a restriction applies to imported products (including internet sales). Inks are imported or purchased by internet and distributed freely in the EU, therefore harmonised measures are needed to ensure same protection level in the EU.

SEAC

SEAC recognises that the placing on the market and use of tattoo inks takes place Union-wide and hence, any measure aiming to effectively reduce the risks for the general public needs to be taken in all Member States of the European Union (as well as the 3 EEA members: Norway, Iceland and Liechtenstein). At present, the level of protection differs among Member States.

The Council of Europe resolutions ResAP(2003)2 and ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up are non-binding recommendations to its signatories (including many EEA Member States). Seven Member States within the European Union (Belgium, France, Germany, the Netherlands, Spain, Slovenia and Sweden) as well as 2 EEA Members (Norway and Liechtenstein) have already implemented national legislation on tattoos based on either one of the two Council of Europe resolutions, and have gathered experience in enforcing it. Three other EU Member States (Austria, Denmark and Latvia) have prepared draft legislation and notified the Commission. In addition, among the Member States that have implemented the Council of Europe resolutions, there are some differences in the application of specific concentration limits for impurities. The requirements for labelling of tattoo inks also differ (JRC 2015a).

The majority of EU Member States (21 of 28) currently have no legislation in place to protect the general public from risks of hazardous chemicals in tattoo inks. Hence, the level of protection is different across the Union. The proposed restriction options aim to set equally high standards of health protection with regard to the presence of hazardous substances in tattoo inks throughout the Union. SEAC agrees that the proposed restriction options are appropriate to harmonise the level of health protection across the Union.

In addition, the proposed restriction will apply a set of common requirements across all affected supply chains at the EU level. Such common provisions will enhance clarity for stakeholders in the supply chain (including importers of inks) and the free movement of goods within the EEA.

Levels of non-compliance identified via surveillance projects by those countries that have already implemented legislation is in the range of 30-50% for tattoo inks and up to 20% for PMU (JRC 2015b). The currently reported levels of non-compliance provide additional justification for a Union-wide measure. Non-compliance in those countries that have implemented ResAP(2003)2 or ResAP(2008)1 may be partly due to absence of ResAP requirements on tattoo inks in a larger part of the EU territory which may increase the availability on the EU market of tattoo inks not complying with ResAP.

Also see the opinion of RAC.

B.3. JUSTIFICATION WHETHER THE SUGGESTED RESTRICTION IS THE MOST APPROPRIATE EU WIDE MEASURE

Justification for the opinion of SEAC and RAC

B.3.1. Scope including derogations

Justification for the opinion of RAC

B.3.1.1. Summary of proposal:

The Dossier Submitter (ECHA in particular) was requested by the European Commission to prepare an Annex XV restriction proposal restricting the placing on the market and use of certain substances in tattoo inks and permanent make-up. The Dossier Submitter has analysed the appropriateness of other risk management options, including legislative and non-legislative measures, to address the risks from hazardous chemicals in tattoo inks. Specifically, measures in the scope of the EU Cosmetic Products Regulation (CPR), the Biocidal Products Regulation (BPR), the Classification, Labelling and Packaging (CLP) Regulation, the EU Ecolabel Regulation, standalone legislation on tattoo inks and other voluntary actions were analysed. The Dossier Submitter considers none of these options to be appropriate to address the risks of hazardous substances in tattoo inks, because they are not as practical, effective or consistent and harmonised as a restriction under REACH. As a result, the Dossier Submitter proposed and further evaluated the effectiveness, practicality and monitorability of two restriction options: Restriction option 1 (RO1) and Restriction option 2 (RO2). The options differ primarily in terms of the

proposed concentration limits for selected substance groups and how the links with the CPR are managed.

a) Concentration limits

The proposed concentration limits are derived on the basis of the substances hazard classification, their presence in the CPR or the results of a quantitative or qualitative risk assessment. Other considerations such as the achievability of these concentration limits, the limit of detection in prevailing analytical methods, the availability of technically feasible alternatives and other socio-economic considerations are also taken into account. In some cases, several considerations are taken into account in the setting of the limit. Table 7 presents the concentration limits for each option in brief.

Derogations

- Selected colourants

The proposed restriction options take into account the availability of alternatives, in particular for colourants which industry will find difficult to substitute. For example, Pigment Blue 15:3 and Pigment Green 7 are essential colourants in tattoo inks, which according to stakeholder reports, do not have technically feasible alternatives presenting lower risk to human health. Furthermore, risk for these substances cannot be demonstrated with the currently available information.

The remaining colourants proposed to be excluded from the restriction on CPR Annex II substances (see Supplementary Table B), are colourants which are banned for use in hair colours (CPR, Annex II) but allowed in all cosmetic products (CPR, Annex IV). They are proposed to be excluded because many of the pigments prohibited in hair colours were included in Annex II of the CPR on the basis of the cosmetic industry not providing relevant information to justify continued use in the hair dyes application.

- Classified substances for inhalation exposure only: As risks associated with the inhalation route only are not relevant for tattoo and PMU exposure, substances classified as carcinogenic via this route only are derogated.
- Substances that are gases at standard temperature and pressure (20 °C and standard pressure of 101.3 kPa, or generate a vapour pressure of more than 300 kPa at temperature of 50°C), since they are not expected to be found in tattoo inks due to their physical state.

b) Labelling requirements

Both restriction options foresee a labelling requirements for tattoo inks and PMU, which are similar to the CoE resolution (with respect to requesting information on hazardous substances) and consistent with the CLP Regulation. The labelling requirements extend to not only to the substances that are included in the scope of the restriction but also to any other substances that may present risk to human health. This would ensure that these substances would be listed to inform consumers who intend to undergo a tattoo procedure. This is particularly important in the case of tattoo inks when hazardous substances are injected under the skin and may have unforeseen consequences due to this route of exposure. It is also important that consumers who are already (cross)sensitised to certain substances can check to see these are not in tattoo inks.

c) Additional conditions

- Colourants in Annex IV of CPR with conditions on their use

Some colourants used in cosmetic products have been shown to pose a risk to human health when applied to the skin in concentrations exceeding the maximum allowed concentrations specified in Annex IV of CPR or when not meeting the other conditions in columns "h" to "i" of the Annex (e.g., purity requirements). (See Supplementary Table E.) Therefore, given the similarities in exposure potential, a comparable restriction for use of these colourants in tattoo inks and PMU is proposed.

- Restriction on the use of tattoo inks not meeting the requirements by tattoo artists

As it is possible for tattoo artists to stockpile pigments in powered form and mix tattoo inks, the restriction puts the onus on tattoo artists and PMU practitioners to ensure that non-compliant inks are not used for tattoo or PMU purposes by proposing that inks not meeting the restriction requirements are not used in tattoo and PMU procedures.

- Transitional period

Given the number of EU Member States who already have national legislation, the availability of inks meeting the ResAP requirements and the similarities between RO1 (and less strict requirements of RO2) and ResAP, it is anticipated that a transitional period of one year will allow sufficient time for actors in the supply chain to meet the proposed requirements.

- Definitions and other enforcement considerations

To assist with enforcement, the proposed restriction text includes definitions of tattoo and PMU practices. The dossier also lists the substances included in the scope (see Supplementary tables A-E in the Background Document) These lists also include information on whether the substances have been found in tattoo inks and PMU according to surveillance results or literature review as per JRC report (JRC, 2015b). This will assist enforcement authorities to focus their initial efforts checking compliance on the presence of key substances.

d) Linkages with the CPR

The proposed restriction scope covers a number of substances included in the CPR (Annex II and Annex IV). The two restriction options differ with respect to the type of link established by the proposed REACH entry and the CPR:

- RO1 proposes a dynamic link (which ensures any future updates are reflected in the REACH measure),
- RO2 proposes a static link, ensuring that any new substances are added to the restriction after specific assessment of their risks to human health when injected intradermally, the availability of alternative, and technical feasibility for achieving the proposed concentration limits.

e) Other risks related to tattooing

This restriction proposal is limited to addressing risks related to chemicals that can be addressed under REACH. It should be noted that all the aspects not covered by the restriction proposal such as general hygiene requirements or chemicals with no hazard classification can continue to be regulated at the Member State level provided that such national requirements comply with the Treaty provisions on free movement and provision of services.

During the opinion-development process, the following changes to the proposed restriction wording were introduced by the Dossier Submitter as a result of Forum advice:

- Proposed derogation for gaseous substances: as substances that are gaseous (at temperature of 20°C and standard pressure of 101,3 kPa, or generate a vapour pressure of more than 300 kPa at temperature of 50°C) are excluded from the scope as they are not expected to be in tattoo inks. A definition of gaseous substances is included in the wording of the restriction.
- Labelling requirements: The requirement to list substances "present" in tattoo inks was revised to those "used"[42] in tattoo inks to reduce the regulatory burden on industry. The requirement to list the name of the substances in the scope of the restriction was amended to make it necessary to include the substances when they are found in tattoo inks, i.e., "The name of any additional substances covered by this restriction that are used in the tattoo ink." In addition, it was clarified that the person performing this procedure shall make the information on the label available to any person before they undergo the tattooing procedure. It was also clarified that only substances classified in Annex VI of CLP are subject to the labelling requirement and not those meeting the criteria for classification (self-classified).
- Definition of tattoo procedure: Additional popular terms for PMU procedures were included in the definition. It was also clarified that the intradermal injection is one way of introducing tattoo ink into the skin.
- Addition of labelling requirements for tattoo inks containing chromium and nickel.
- Ensuring that the derogation of the pigments in Table B is interpreted to be valid

[42] Art. 3(24) of REACH use "means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation." This in effect means that it is not required to include on the label not intentionally added substances (e.g., an impurity) if they are present in lower concentrations than proposed to be restricted under RO1 or RO2. This will diminish the need for those placing tattoo inks on the market to conduct extensive and costly testing.

to such time in the future until when a relevant harmonised classification (i.e., included in the scope of the proposed restrictions, e.g., carcinogenic, skin sensitiser) is made.

Reduction of the concentration limit proposed for soluble copper to 0.25% w/w was introduced in line with Public Consultation comment (#1916) and additional information on copper kinetics in humans provided by the Dossier Submitter.

Reduction of the concentration limit for sink sensitisers in RO2 to be in line with the concentration limits that trigger labelling requirement under the CLP: i.e., 0.1% for category 1/1B sensitisers and ≥ 0.01% for category 1A sensitisers.

B.3.1.2. RAC conclusion(s):

RAC agrees with the Dossier Submitter that a restriction under REACH is the most appropriate EU wide measure. RAC also agrees with the Dossier Submitter's proposals for **scope, labelling requirements and additional conditions**[43] but it is proposing different concentration limits for selected substances (see RAC modified RO1). These changes are based on RAC's evaluation of the Dossier Submitter's risk assessment for the substance groups and individual substances (see Appendix 3 and 4 to this opinion for details). Information on the practicality of some of the limits proposed by the Dossier Submitter was challenged in the Public Consultation and these comments have been taken into account in RAC's assessment (see the RCOM for further details).

RAC supports **derogations** of substances classified due to effects seen only following inhalation exposure, and of the substances that are gases at standard temperature and pressure, but has a different view on colourants proposed to be exempted from the proposed restriction on substances listed on Annex II to the CPR. Namely, RAC does not support derogation for these pigments, including two phthalocyanine colourants Pigment Green 7 and Pigment Blue 15:3, due to the limited information available on hazards and risks (please see section B.3.1.3 for justification).

Regarding the **linkage with the CPR**, RAC supports a dynamic link (as proposed in RO1). RAC is aware that this option has some drawbacks but considers that they are outweighed by the benefits for human health (further discussed in the section below). RAC finds that there is no scientific basis for a transitional period, and proposes that any changes to the CPR are adopted in this restriction without delay.

Regarding the **linkage with the CLP**, both RO1 and RO2, as well as RAC modified RO1 are dynamically linked to Part 3 of Annex VI of Regulation (EC) No 1272/2008. RAC supports this linkage and proposes that any changes to Part 3 become applicable to tattoo inks as soon as they take effect under CLP. RAC stresses that a dynamic link with CLP is necessary to make sure that action to protect human health from risks related to tattoo inks reflect the latest information on serious health hazards and action is taken quickly.

With respect to **other risks related to tattooing**, RAC acknowledges that the aspects

[43] Regarding the colourants in Annex IV of CPR with conditions on their use, restriction on the use of tattoo inks not meeting the requirements by tattoo artists, transitional period, and definitions and other enforcement considerations

not covered by the restriction proposal, such as general hygiene requirements or chemicals without harmonised classification, can continue to be regulated at the Member State level.

B.3.1.3. Key elements underpinning the RAC conclusion(s):

RAC considers that the proposed restriction under REACH is the most appropriate EU wide measure, since it has wider scope and effectiveness is expected to be higher compared to other risk management options discussed in the section B.1.4.3.

Scope

As already discussed in section B.1.1.3, RAC supports the wide scope of this restriction proposal, since it is the only way to cover the variety of potentially hazardous substances used in tattoo inks, out of which only part have been identified in commercial tattoo inks so far, and to prevent substitution with hazardous alternatives in the future.

RAC also agrees to take into account assessments conducted under other legislation (i.e., CPR and national regulations based on CoE ResAP(2008)1), and include in the scope substances restricted in these legislations. Taking precautionary approach, this includes substances restricted without traceable or recently revised opinions of the Scientific Committee on Consumer Safety (SCCS) or its predecessors.

RAC, nevertheless, points out that some hazardous substances will not be covered at the present moment by the scope of proposed restriction. The reasons, examples and potential solutions for this issue have been discussed in the sections B.1.1.3 and B.1.2.4, and the Dossier Submitter listed substances considered relevant for any future evaluation of the restriction in Appendix D1 of the Background Document.

Concentration limits (CLs)

The Dossier Submitter proposed different CLs under RO1 and RO2, with the main differences concerning CPR substances in the scope (i.e. Annex II and Annex IV with use restriction in column "g") and substances with harmonised classification (with RO1 being generally stricter). For some substances the CLs are risk-based[44], for others a practical approach has been proposed[45], and for some substances, CLs were transferred from other legislation[46] or CoE ResAP(2008)1[47], as examples of technically achievable limits. The Dossier Submitter took into account technical feasibility and information on the limit of detection of the currently used methods. During the work on this restriction, RAC has found necessary to develop a concept of practical concentration limit.[48]

The RO1, in general, follows existing national legislation in nine EEA Member States with national legislation on tattoo inks. CLs for carcinogens, mutagens and substances restricted in the CPR (Annex II and Annex IV column "g") are set to LoDs of available analytical methods which in practice means prohibition. For skin sensitisers and skin/eye

[44] carcinogens/mutagens under RO1, reproductive toxicants, methanol, arsenic, barium, copper

[45] skin sensitisers, skin/eye irritants/corrosives, azo colourants, PAAs

[46] CPR substances under RO1 and PAHs

[47] cadmium, antimony, tin, mercury

[48] See footnote 30

irritants/corrosives a practical limit of 0.1% is set to prevent intentional use and for reprotoxic substances a CL based on risk assessment is set. In addition, specific concentration limits are set for PAHs, selected PAAs and substances in Table 3 of CoE ResAP(2008)1.

Under RO2, the CLs for substances classified as carcinogens, mutagens, skin sensitisers and skin/eye irritants/corrosives are proposed to be the GCL or SCL of the substances set in the CLP Regulation, while for substances on Annex II and IV (column "g") of the CPR a practical limit of 0.1% w/w is proposed.

For colourants restricted with conditions in Annex IV of the CPR (columns "h" and "i"), PAHs, azo colourants and PAAs in the scope, methanol and impurities from Table 3 of CoE ResAP(2008)1, same CLs are proposed in RO1 and RO2.

Under RO1, the CLs are more protective, but more difficult to enforce compared to CLs under RO2, as pointed out in the Forum advice (see section on enforcement). Another major concern with RO1 is that the unavoidable presence of some impurities, not intentionally added to the inks, which could result in some inks currently allowed on the market to not be allowed due to the proposed restriction.[49]

The main reason why the Dossier Submitter proposed RO2 was to prevent tattoo inks with trace amounts of not yet identified hazardous impurities becoming non-compliant. Namely, since a full list of impurities is unknown, there is a risk that the proposed RO1 would render a large share of tattoo inks currently on the market and compliant according to national legislation, as non-compliant. Therefore, RO2, with higher practical limit (0.1% w/w) for CPR substances in scope and the CLP limits for those with relevant harmonised classification, is proposed.

RO2 is also expected to be simpler in its content and format, for stakeholders (see section on enforcement). RAC, nevertheless, considers that RO2, although more easily enforceable, is generally not protective enough.

In addition to the Restriction Options proposed by the Dossier Submitter under RO1 and RO2, RAC proposes a modification of RO1 concentration limits. This is needed because RAC considers that the CLs for some substances in RO1 or RO2 are not protective enough, and that for other substances more practicable CLs could be proposed, while minimising risk for human health. Namely, RAC takes into account:

[49] These traces are dealt with in a practical manner in national legislation on the basis of Article 17 of the CPR: "The non-intended presence of a small quantity of a prohibited substance, stemming from impurities of natural or synthetic ingredients, the manufacturing process, storage, migration from packaging, which is technically unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3.", where Article 3 states that "a cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use". However, this way of enforcement is not feasible under the setting of Annex XVII of REACH.

- that a total ban ("shall not contain", i.e. CLs set to LoDs), proposed for some substances/groups of substances under RO1, is more difficult to enforce than specific concentration limit;[50]
- that some CLs under both RO1 and RO2 are not protective enough (e.g. skin sensitisers, skin/eye irritants, cobalt);
- that a correction factor for oral absorption in deriving some DNELs is needed, regarding 100% assumed absorption of intradermally applied chemicals (copper, soluble barium salts);
- that for some substances, in addition to risk-based, a practical CL is needed with respect to technical achievability (e.g. arsenic and PAAs);
- the Forum's advice and comments received during the Public Consultation.

In RAC modified RO1, both risk-based and practical CLs are proposed for all substances/groups of substances in the scope (Table 7). RAC took into account the availability of analytical methods but based practical CLs on technical achievability. In addition, RAC took into account the advice of the Forum related to the need for practical concentration limits and the information provided in the public consultation.

RAC points out that for substances for which it was not possible to perform a risk assessment for the present restriction proposal, an assessment should be done in the future evaluation of the restriction. The same applies for impurities not yet identified in tattoo inks, if they appear in a concentration higher than respective CL proposed.

Derogations

RAC assessed the Dossier Submitter's proposal to derogate the following substances:

- 21 colourants which are banned for use in hair colours (CPR, Annex II) but allowed in all other cosmetic products (CPR, Annex IV):
  - two phthalocyanine pigments, Pigment Blue 15:3 and Pigment Green 7, for which a concern was raised by industry that they are essential for tattooing, and there are no technically adequate alternatives;
  - 19 other, non-phthalocyanine colourants, for which no concern regarding their potential restriction was raised by industry .
- Substances classified for inhalation exposure only: As risks associated with the inhalation route only are not relevant for those getting a tattoo, substances classified as carcinogenic via this route only are derogated (e.g., titanium dioxide). Such substances might create a risk for tattoo artists, but health hazards related to

[50] Forum points out that "Specific limit value would be easier to enforce than a totally banned substance. If no limit value is set, non-compliance depends on limit of detection of the available method chosen by the national enforcement authority. Member states use different labs and different labs may have different limits of detection and harmonization in the community could be jeopardized. Also, experience of enforcing restrictions and other legislations where no limit value is set tells us that there is more room for economic operators and potential defendants to question our results if there is no specific limit value."

occupational exposure are out of the scope of this proposal.

- Substances that are gases at standard temperature and pressure.

RAC is of the opinion that substances classified due to effects seen only following inhalation exposure, and not induced by exposure through any other route of exposure (dermal, oral) should be derogated since they do not pose risk for tattooed persons. RAC also agrees to derogate substances that are gases at standard temperature and pressure, since they are not expected to be found in tattoo inks due to their physical state.

Regarding the 21 colourant proposed by the Dossier Submitter to be excluded from the restriction on CPR Annex II substances, they were included in this Annex because of the concern that their use in hair dyes could be related to increased risk of cancer, primarily in the urinary bladder (e.g., Gago-Dominguez et al., 2001; Miller and Bartsch, 2001; Harling et al., 2010). Since epidemiological data underpinning this concern could not specifically indicate which colourants were responsible for the increased risk, the Commission proceeded with a ban on all permanent and non-permanent hair dyes for which the cosmetics industry did not submit any safety files and those hair dyes for which the SCCS had given a negative opinion (Ref. Ares(2015)4346889 - 16/10/2015). The colourants are proposed by the Dossier Submitter to be excluded from the restriction because they do not have harmonised classification and while they are banned in hair dyes (listed in Annex II of the CPR), at the same time they are allowed for use in all other cosmetic products (Annex IV of the CPR, some with conditions on use). The reasons why they are listed in Annex IV of the CPR are not available. This situation, however, creates inconsistency in their legal status in different EU Member States with national legislation, as stated in the Background Document.

After summarising the available toxicological data for the 21 colourant proposed by the Dossier Submitter to be excluded from the restriction on CPR Annex II substances (more detailed analysis was not possible due to unavailability of original reports and lack of more extensive study descriptions), RAC considers that the risk of cancer indicated by epidemiological studies cannot be ruled out for the majority of these colourants.

As pointed out in the Background Document, experimental toxicological data on carcinogenicity of these colourants are deficient for 16 out of 21 colourants (see Appendix B.12 of the Background Document for further details). From the five colourants for which experimental data are of sufficient quality to draw conclusions (FD&C Red 4, Acid Red 27, Acid Blue 3, Fast Green FCF, Acid Red 51), three were negative (FD&C Red 4, Acid Red 27 and Acid Blue 3). An increased incidence of thyroid neoplasms observed in oral studies with Acid Red 51 was interpreted by EFSA as of limited human relevance (EFSA, 2011). For Fast Green FCF, although carcinogenicity was negative in oral studies, a high incidence of fibrosarcoma was reported in rats after long-term subcutaneous injections (Hansen et al., 1966; Hesselbach and O'Gara, 1960). However, for three colourants for which experimental data did not indicate risk for carcinogenicity (i.e., FD&C Red 4, Acid Red 27 and Acid Blue 3), as well as for Acid Red 51, potential risk of other health hazards was noted. FD&C Red 4 is banned by the US FDA (in 1976) as a colour in food, ingested drugs and cosmetics, because of adverse effects observed in the urinary bladder (chronic follicular cystitis with haematomaous projections into the bladder), adrenals (atrophy of

the zona glomerulosa) and liver (haemosiderotic focal lesions) in long-term oral study in dogs (Deshpande 2002; US FDA 21CFR81.10). Acid Red 27 (Amaranth) is permitted as a food additive in the EU under the restricted levels (0.003% to 0.01%), but embryotoxicity has been observed in some studies (Collins and McLaughlin, 1972, 1973; EFSA, 2010), and available data indicate it could trigger classification as eye irritant cat. 2. Acid Blue 3 is also approved as a food colourant (E 131) in the EU, and as a diagnostic tool in medicine. However, allergic reactions have been reported in patients after parenteral exposure, and an EFSA Panel (EFSA, 2013) noted that the application of this colourant in various fields (cosmetics, textiles, paints, inks) could potentially cause sensitisation. Acid Red 51 was non-mutagenic in oral *in vivo* studies, but it showed clastogenicity following *i.p.* administration (EFSA, 2011).

Non-carcinogenic hazards relevant for this restriction proposal cannot be ruled out for the following colourants as well: local (skin) or systemic allergic reactions for Solvent Violet 16 and Acid Yellow 73), and irritant or corrosive skin or eye effects for Pigment Red 83, Acid Yellow 73 and Acid Red 87. Fast Green FCF was mutagenic in *in vitro* bacterial and mammalian cell assays, and there are reports indicating possible risk of skin sensitisation in tattooed people.

RAC points out that carcinogenic potential for the majority of these chemicals was tested via the oral route (exceptions are FD&C Red 4 and Pigment Blue 15 for which long-term data with subcutaneous administration exists), which is of limited relevance for risk assessment of the dermal exposure route related to hair dye exposure in human population or for intradermal application during tattooing procedure. Namely, for a majority of these colourants low or very low oral absorption was found (in toxicokinetic studies) or predicted (based on physico-chemical properties) (please see Table 132 in Appendix B.12 of the Background Document).

The uncertainty related to low oral absorption of these colourants also applies to Pigment Blue 15:3 (CI 74160; 29H,31H-phthalocyaninato(2-)-N29,N30,N31,N32 copper) and Pigment Green 7 (CI 74260; polychloro copper phthalocyanine), which are copper phthalocyanine colourants. Pigment Blue 15:3 represents the unmodified version of the molecule, while Pigment Green 7 is chlorinated 14 to 16 fold per phthalocyanine (SIAR, 2005). According to information provided in the Registration Dossiers, SIAR (2005) report and the Background Document, it could be concluded that both colourants are of low acute and repeated-dose toxicity, and apparently without irritant or sensitisation potential. However, regarding genotoxicity, carcinogenicity and reproductive toxicity, the toxicological data are too deficient to allow a reliable conclusion (for further details on toxicological information on these colourants please see Appendix B.12 of the Background Document). Briefly, genotoxicity testing did not include a standard battery of assays.[51] In

[51] Standard three-test battery of *in vitro* tests, containing Ames test, *in vitro* mammalian cell gene-mutation test and *in vitro* test for structural chromosome damage and aneuploidy, are usually required for chemicals' and biocidal products' assessment (Corvi and Madia, 2017). Two-test battery could be also applied (Ames test and *in vitro* test for chromosomal adverse effects), but should include testing for detection of aneuploidy (e.g., *in vitro* micronucleus test instead of *in vitro* mammalian chromosomal aberration test).

the case of Pigment Green 7, gene mutation assay in mammalian cells or *in vivo* assays are not available, and the potential for inducing aneuploidy was not tested. In the case of Pigment Blue 15, the testing was more extensive: negative results were obtained in an Ames test, in an *in vitro* test for chromosomal aberrations and in a mouse spot test (which can detect both somatic mutations and chromosomal aberrations). Nevertheless, the usefulness of the mouse spot test in toxicology is considered to be limited by restrictions in e.g. toxicokinetics (transplacental transfer of a substance is required) or sensitivity (small number of genes is tested) (Wahnschaffe et al., 2005). Regarding reproductive toxicity, only a screening test (OECD 421) is available (and only for Pigment Blue 15), and, even more importantly, RAC points out that oral or dermal studies are of limited relevance for risk assessment of the intradermal application of these colourants since it is considered that copper phthalocyanine-based pigments are not absorbed after ingestion and after skin contact (Registration Dossiers for Pigment Blue 15:3 and Pigment Green 7)[52]. Carcinogenicity data for Pigment Blue 15 (for Pigment Green 7 no carcinogenicity study is available) were obtained following subcutaneous exposure route, but with significant limitations in study design (only one dose tested in 17 animals, short duration of the study, i.e., 34 weeks). As already discussed in section B.1.2.1.3, although these colourants have extremely low solubility in aqueous solutions, fate and bioavailability of phagocytosed phthalocyanine pigment particles is not known.

Therefore, RAC is of the opinion that the exemption of these 21 colourants cannot be based on their non-hazardous profile, primarily due to lack of adequate information on their hazard properties and risk for human health.

During the ECHA Call for Evidence (ECHA CfE, 2016a) and the Public Consultation, no concern was raised regarding the potential restriction of 19 non-phthalocyanine colourants. The reason could be a limited use of these colourants in tattoo inks or availability of alternatives for those which are used, as some answers during the Public Consultation indicated. Since in the available literature and other information sources there is a lack of adequate information on hazard properties and risk for human health for these **19 non-phthalocyanine colourants**, and during the ECHA CfE and the Public Consultation no concern was raised regarding their restriction, **RAC does not support their derogation**.

On the other hand, RAC recognises that during the ECHA Call for Evidence and the Public Consultation a concern was raised by industry that two phthalocyanine pigments, Pigment Blue 15:3 and Pigment Green 7, are essential for tattooing and there are no, technically adequate alternatives.

[52] This is supported by the fact that, as stated in the Registration Dossiers for Pigment Blue 15 and Pigment Green 7, "the National Toxicology Program (NTP) decided not to conduct a long term bioassay on phthalocyanine blue and green pigments based upon the results of their own 90-day feeding study conducted on mice and rats. During this study, mice and rats were fed with phthalocyanine pigments in their diet at concentrations of 0.3 to 5%. No signs of toxicity were observed. The NTP concluded that the outcome of this 90-day study together with the insolubility of the test substance and the minimal changes in tissue copper residues strongly suggest that the material is not bioavailable."

In addition to Pigment Blue 15:3 and Pigment Green 7, other blue and green pigments have been reported to be used in tattoo inks (see Appendix B.12 in the Background Document with a non-exhaustive list based on the information from the Background Document, open literature and internet sources, including technical data from producer/supplier Internet pages).

RAC concludes that although there are some blue pigments for which a low hazard profile could be expected, specific information on the hazardous properties and technical feasibility of these alternatives are not available or are very limited. Other pigments are either of higher concern for human health or their technical characteristics are reported inferior compared to Pigment Blue 15:3.

As for Pigment Green 7, it has been largely replaced with Pigment Green 36 (which is not in the scope of this restriction since it has no harmonised classification and it is not listed on Annex II or Annex IV of the CPR), a brominated version of Pigment Green 7. Not much data is available for Pigment Green 36. According to the Registration Dossier, this pigment was not genotoxic in bacterial gene mutation assay. For all other endpoints, read-across from Pigment Blue 15 was applied. Regarding bromide ion, it is known to be toxic to humans if taken in excessive amounts (e.g., in the range of 0.5-1 g/day orally, following chronic exposure, 2-4 weeks or longer).[53] Although rapid and extensive release of bromide ion from phthalocyanine pigment is not expected, especially not in the extent to cause systemic toxicity, brominated Pigment Green 36 cannot be considered as a less hazardous alternative to chlorinated Pigment Green 7. Regarding other green pigments reported to be used in tattoo inks (see a non-exhaustive list in Appendix B.12 in the Background Document), RAC considers that limited information on their human health hazards and technical characteristics do not indicate less hazardous and, at the same time, technically feasible alternatives to Pigment Green 7.

In conclusion, since the data on health hazard and risk profile of the two phthalocyanine colourants, Pigment Blue 15:3 and Pigment Green 7, are too limited, RAC cannot support their derogation.[54]

Nevertheless, RAC is aware that a concern was raised by industry that these two colourants are essential for tattooing, without technically adequate alternatives, that alternatives with a more concerning hazard profile are presently used in blue and green inks, and that data on health hazards and risks and technical feasibility of potential alternatives are deficient.

Labelling requirements

RAC considers that the labelling requirements proposed by the Dossier Submitter are appropriate. They are sufficient to facilitate implementation of the restriction as well as to permit investigation of exposure and risks linked with tattoo in the future.

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[53] Chronic excessive exposure may produce a toxic syndrome called "bromism", characterized by behavioural changes, hallucinations, psychosis, ataxia, irritability, headache, and confusion etc. (POISINDEX, 2018).

[54] RAC notes that if derogation for these two colourants is, nevertheless, granted, they will cease to be derogated in the event they receive harmonised classification relevant for the scope of the proposed restriction.

RAC also notes that the labelling requirements proposed by this restriction will not be the only ones regulating labelling of tattoo inks since requirements of other legislations like those mentioned above or the labelling requirement of Regulation (EC) No 1272 will also have to be observed.

Additional conditions

- Colourants in Annex IV of CPR with conditions on their use

As stated previously (section B.1.2.3), RAC supports the Dossier Submitter's proposal to include in the scope colourants listed in Annex IV of the CPR with additional conditions stated in columns "h" and "i". According to the proposed scope, these conditions only apply if a lower concentration limit for a colourant or its impurities is not specified in paragraphs 1 and 2 of the scope. Nevertheless, RAC points out that under the CPR these conditions were derived for dermal exposure, while risk assessment for intradermal exposure route cannot be performed due to knowledge gaps at the present moment. This issue, therefore, presents an uncertainty which is recommended to be addressed in future restriction review, i.e. as soon as new data become available.

- Restriction on the use of tattoo inks not meeting the requirements by tattoo artists

RAC considers that this condition is well justified by the Dossier Submitter and agrees with their proposal to put the onus on tattoo artists/practitioners to ensure that non-compliant inks are not used for tattooing procedures.

- Transitional period

RAC agrees with the Dossier Submitter that a transitional period of one year will allow sufficient time for actors in the supply chain to meet the proposed requirements as well as it will accelerate a full implementation of this restriction. In the opinion of RAC, assuming that production of non-compliant inks will stop immediately after adoption of this restriction, 12 months is sufficient for the industry to comply.

It has been noted that tattoo manufactures submitted information during the Public Consultation stating that testing and reformulation of tattoo inks needs more time than the currently proposed transition period of 1 year. However, a longer transitional period will result in longer exposure to tattoo inks containing hazardous substances. Therefore, RAC is supportive of 1 year transitional period as proposed by the Dossier Submitter.

- Definitions

RAC notes that the restriction proposal provides clear definitions of tattoo and PMU practices, which are a prerequisite for enforcement. RAC further notes that requirements of CoE ResAP(2008)1 have been already implemented in national regulation in several Member States and that the proposed restriction options to a large degree reflect these requirements. In the opinion of RAC, the Dossier Submitter provided all required definitions and considerable amount of information, which will facilitate enforcement based on experience of Member States, which already have national legislation on tattoo inks. The considerable work has been done to provide concentration limits (CL) of hazardous substances in tattoo inks, including CLs set based on quantitative risk assessment and practical CLs based on qualitative approach.

The enforceability of the restriction has been also strengthen by taking into account in the scope of restriction recommendations provided in advise of the ECHA Forum for Exchange of Information on Enforcement.

Linkages with the CPR

Under RO1 a **dynamic linkage** is proposed by the Dossier Submitter, which is reflected in the text of the scope (under RO1) referring directly to CPR Annex II and Annex IV. An advantage of this option is that future changes to CPR annexes apply directly to the restriction, without delay. Disadvantages are that this option does not allow an assessment of technical feasibility for achieving the proposed concentration limits as well as the analysis of alternatives, and that potential legislative gaps could arise[55].

Under RO2 a **static link** is proposed by the Dossier Submitter, i.e. that only substances on Annex II and Annex IV (columns g-i) at the time of the writing of the restriction dossier are included in the scope. Advantages of this option are that it allows risk assessment for individual substances/group of substances and an assessment of technical feasibility and analysis of alternatives, and that it requires less cross-reference to external resources (other regulations). A disadvantage is that for substances restricted by the CPR's future updates, a new Annex XVII restriction proposal is required, resulting in a time lag before substances in Annex II or IV of the CPR are banned in tattoo inks.

RAC prefers a dynamic link with the CPR, since this option, in contrast to a static link, provides faster regulation of hazardous substances without harmonised classification, and is, therefore, more protective for human health.

Regarding drawbacks of a dynamic link, RAC points out that:

- individual risk assessment has not been performed for a vast majority of substances prohibited by the CPR (Annex II and Annex IV column g), and a group approach was applied, instead;
- potential legislative gaps are recommended to be checked for during regular restriction updates, including introduction of new specific limits if necessary.

Linkage with the CLP

RAC points out that if a substance listed in Table A of the restriction proposal becomes classified as CM, SS, etc., it will be subject to the restriction.

[55] For example, a hazardous colorant could be removed from Annex IV because its safe use can no longer be demonstrated, but in that way it will no longer be banned for use in tattoo inks unless it is added to Annex II of the CPR or has a harmonised classification relevant for this restriction proposal. Namely, according to the CPR (Article 14), cosmetic products must not contain colorants other than those listed in Annex IV (and respecting conditions laid down in that Annex). Therefore, if a colourant in not listed in Annex IV of the CPR it is automatically not allowed to be used as a colourant in a cosmetic product, which does not apply to a tattoo ink product.

Justification for the opinion of SEAC

B.3.1.4. SEAC conclusion(s):

Overall, the analysis conducted has provided sufficient justification for SEAC to conclude that the proposed restriction is the most appropriate EU-wide measure to address the risk from hazardous chemicals in tattoo inks. SEAC agrees with the Dossier Submitter's conclusion that the other risk management options assessed are not as appropriate as a restriction under REACH due to limitations in scope and effectiveness. An amendment of the CPR or standalone legislation could also be effective legal measures and were mentioned by some stakeholders in the Public Consultation and in the Forum advice as a providing a more logical approach since the tattoo ink market is not well acquainted with REACH.

SEAC however considers the option of a standalone legislation or an amendment of the CPR less appropriate options as these would require a longer and more complex procedure for the legislative process compared to the proposed restriction under REACH.

SEAC in general agrees with the scope of the restriction as proposed by the Dossier Submitter including the adaptations made during the opinion development.

SEAC has reservations with respect to the technical feasibility and ease of enforcement of some **concentration limits** proposed in RO1. SEAC supports RAC's proposal for modified RO1 with respect to concentration limits for selected substances based on risk assessment, enforceability and feasibility considerations.

Taking into account information received during the public consultations on the Annex XV Dossier and the SEAC draft opinion, including from five tattoo ink formulators/manufacturers, SEAC recommends a two-year time-limited **derogation** of Pigment Green 7 and Pigment Blue 15:3, to provide sufficient time to the tattoo industry to transition to alternatives. SEAC also takes into account RAC's view that that alternatives with a more concerning hazard profile are presently used in blue and green inks and its recommendation that further assessment is made of the risks from alternatives by industry and authorities.

SEAC does not support derogations of the other 19 colourants listed in supplementary Table B of the Background Document since the Public Consultation revealed only some of the pigments are used and for all of them alternatives are available. SEAC agrees with the proposed **labelling requirements** for tattoo inks including the changes made in the proposal during the opinion development as a result of Forum advice or public consultation comments.

SEAC supports a 1 year **transitional period** as a reasonable timeframe for implementation of the restriction.

Taking several aspects into consideration, SEAC supports a dynamic link with CLP for substances included due to relevant harmonised classifications. SEAC has a slight preference for a **static link with the CPR** as it has the advantage of regulating appropriately chemicals for their use in tattoo inks, taking into account the costs to industry as well as the delay in possible health benefits of the restriction.

B.3.1.5. Key elements underpinning the SEAC conclusion(s):

Prior to asking ECHA to prepare a restriction dossier, the European Commission, following a comparative assessment of several EU-wide risk management options and based on an extensive data gathering,[56] determined that a REACH restriction would be the most suitable EU-wide measure. SEAC was not provided with this previous assessment and therefore could not verify the rationale for this conclusion.

SEAC agrees with the scope of the Dossier Submitter's analyses in which many possible relevant other EU-wide measures have been assessed. SEAC notes that taxation of inks based on their composition was not considered by the Dossier Submitter. Although SEAC considers that there may be some arguments to merit the use of taxation, there is limited scope for their introduction at EU level. Such fiscal measures were not proposed by the Dossier Submitter, and therefore, not further assessed.

The Dossier Submitter explained that currently tattoo inks are outside the **scope of the CPR** because they are injected into the dermis. SEAC notes that the definition of 'cosmetic product', as laid down in article 2.1(a) of the CPR, excludes this route of administration as only substances and mixtures 'intended to be placed in contact with the external parts of the human body' are in the scope. In order to address the risks of hazardous substances in tattoo inks, the CPR Regulation would need substantial changes. The Dossier Submitter has not further assessed the broadness and exact nature of these changes or the amount of work and time needed to implement such changes. SEAC recognises that, in general, extending the scope of the existing CPR to cover also tattoo inks may be legally complicated, time consuming and costly. On the other hand, SEAC considers that extending the scope of CPR to also cover substances in tattoo inks could have efficiencies because of the ease of implementation and enforcement by the same public bodies in Member States that are currently responsible for the cosmetics rules of the CPR[57], since current (and proposed restriction) legislation is closely linked to the CPR (Annex II and IV). Further information for more in-depth assessment is not available to SEAC. Based on the above, SEAC considers that the use of the CPR to regulate risks of hazardous substances in tattoo inks is likely to be a less appropriate option compared to the proposed restriction under REACH, because of the legal complexity of changing the scope of a regulation on cosmetics compared with amending Annex XVII of REACH through a regular regulatory process. SEAC notes however, that for national bodies regulatory management through a CPR amendment might have been a possible approach but SEAC has no further information to assess fully potential advantages and disadvantages.

The Dossier Submitter describes why risks of hazardous substances in tattoo inks are not controlled by the **BPR** (only preservatives are regulated) and **CLP** (does not restrict the

[56] JRC 2015a, JRC 2015b; JRC 2016a, JRC 2016b

[57] In some Member States with national legislation on tattoo inks in place, enforcement bodies responsible for the CPR are also responsible for tattoo inks.

placing on the market of mixtures containing these substances). SEAC agrees with the Dossier Submitter's conclusion that these regulations cannot fully address the identified risks. The BPR provides limited possibilities because of its narrow scope (preservatives used in tattoo inks should already be regulated under BPR but other types of substances could not be) and the CLP Regulation is designed only for hazard classification and communication on hazardous substances and mixtures. As such, the CLP cannot restrict the placing on the market and use of specific substances and mixtures for use in tattoo inks. A harmonised classification under the CLP results in regulatory consequences in other legislation (such as REACH or worker legislation) but for tattoo inks it only invokes labelling requirements and does not restrict the use of specific substances. The EU CLP labelling requirements already apply to tattoo ink mixtures for those substances that exceed the limits for classification as hazardous. CLP labelling of hazardous tattoo ink formulations however is targeted at informing the supply chain and consumers on hazards rather than implementing mitigation measures protecting against human health risks arising from the application of tattoo inks in the skin. Furthermore, as concluded by RAC, some of these CLP limits are not sufficient to mitigate risks. CLP labelling requirements therefore will only to a certain extent inform consumers about hazardous ingredients in tattoo inks and will not sufficiently protect them against risks.

Voluntary actions taken by industry in EU Member States were also included in the analysis of risk management options. The Dossier Submitter concluded that due to the large number of often non-organised operators, as well as the high percentage of non-registered tattoo service providers, it is likely that voluntary measures that effectively control the risk will be difficult to agree and implement uniformly within the EU. SEAC takes note of the JRC reports (JRC 2015b; JRC 2016b) and other information in the Background Document that support the conclusion of the Dossier Submitter. SEAC notes that the questionnaire and literature analysis performed by the JRC revealed a complex EU market with many different manufacturers, distributers and private labels. Furthermore, the Background Document provides information demonstrating a generally low level of sectoral cooperation and organisation (low memberships in associations, as well as the high percentage of non-registered tattoo service providers). In addition, the majority of inks for tattooing available on the European market (70-80%) are manufactured outside the EU (about 20-30% for PMU) and are imported, primarily from the United States. SEAC considers that the low level of organisation in the supply chain and of service providers, the complexity of the EU tattoo inks market and its partial dependence on non-EU manufacturers, is not a favourable situation for implementing a scheme of voluntary actions such as Good Manufacturing practices. For successful implementation of voluntary measures SEAC considers proper sectoral cooperation and organisation as a key element and the aspects mentioned above do not facilitate this. Furthermore, after the Council of Europe introduced their recommendations (ResAP 2003 and ResAP 2008), the tattoo ink sector has not fully adopted these recommendations as has been demonstrated during the surveillance campaigns in various Member States. However, SEAC notes the ResAP is not a binding legislative instrument, and is also not a voluntary industry initiative, and the Background Document contains no information on the reasons for the tattoo ink sector not adopting voluntarily the recommendations.

Overall, SEAC concurs with the Dossier Submitter's assessment that voluntary measures by industry to control the risk from hazardous substances in tattoo inks are unlikely to be effective.

SEAC considers regulatory actions by individual Member States based on the non-binding ResAP recommendations (i.e. national law), as not appropriate to address the EU-wide concern. The ResAP has been in place since 2003 and 2008 and only a minority of EU Member States have adopted (or intended to adopt) the recommendations in national law. Such nationally introduced legal measures address only the identified risks in those Member States having national legislation and not on an EU-wide level in a harmonised and timely manner. SEAC also takes note of RAC's conclusion that the risk management options based on previous Council of Europe recommendations, i.e., CoE ResAP(2003)2 or CoE ResAP(2008)1, do not sufficiently address risks arising from all possible hazardous substances in tattoo inks. Therefore, SEAC agrees with the Dossier Submitter that any restriction options with a scope equivalent to ResAP(2003)2 or ResAP(2008)1 do not need to be assessed further.

The Dossier Submitter also briefly described the use of the **EU Ecolabel Regulation** as a regulatory management option and concludes that it currently does not apply to tattoo inks and it is uncertain whether it will in the future. SEAC considers in theory the EU Ecolabel Regulation could be amended to cover tattoo inks comparable with the coverage of textile products for which the presence of harmful substances was introduced as an exclusion criterion for awarding the ecolabel. SEAC notes the EU ecolabel is a "market-based instrument" whose primary function is to stimulate the supply and demand of products with a reduced environmental (ecological) impact. In general, labels such as the EU ecolabel are known for the level of trust consumers place on them and various studies report on a willingness to pay for eco-labelled products over non-labelled products. SEAC however has no information of the impact on the ecolabel on consumer behaviour in relation to the preference for tattoo inks. SEAC therefore considers that an EU ecolabel would offer no guarantee that all consumers are protected against the risks of tattoo inks. Furthermore it would take time to develop criteria for a tattoo ink ecolabel.

The option of a **standalone EU-wide legislation** on tattoo inks is assessed by the Dossier Submitter. The main advantage of such standalone legislation is that it would offer the possibility to include in one piece of legislation an array of factors that influence the safety of tattoo practices. In particular, different safety aspects (not only chemical, but also microbiological safety) but also possibly training and licensing could be covered in a single harmonised framework. The main disadvantage identified is that it would be difficult and time consuming to negotiate such legislation EU-wide, as the hygiene and certification aspects are normally within the jurisdiction of local and regional authorities. Also, the existence and the nature of these requirements varies substantially among Member States (i.e. in some Member States no legislation is in place while in others, e.g. in the Netherlands, legislation stipulates in detail hygienic measures to be taken by tattoo shops). In the Public Consultation, comments were received that favour a standalone EU-wide legislation. The main argument provided is that aspects such as training, certification, and hygiene requirements are essential for the safety of those who would like to get a tattoo

and hence, should be included in one piece of legislation covering also chemical safety. In addition, comments were received calling for a so-called "positive list", i.e., a list of chemicals allowed in tattoo inks, instead of a restriction. The elements to justify such a list were not provided and SEAC notes that the resources needed to define such a list could be substantial.

The restriction proposal aims to regulate only the chemical risks through REACH and hence, cannot be compared with standalone legislation that would have a broader safety scope. SEAC recognises that, in principle establishing standalone legislation would entail a legally complex and time-consuming process, though would provide a more holistic approach to managing all risks associated with tattooing and tattooing procedures. However, it is outside SEAC's remit to compare the introduction of a new standalone legislation that covers a broader scope with the implementation of a restriction focusing on chemical safety by amendment of Annex XVII of REACH.

a) Concentration limits

SEAC finds that the concentration limits have been set using both risk-based as well as pragmatic considerations (fixed to discourage intentional use). Some concentrations limits have been set in analogy with existing limits for the same substances in other legislation. SEAC notes that, although every concentration limit is well explained and justified, the Dossier Submitter is not consistent in its overall approach how concentration limits are set. For PAAs, the Dossier Submitter explained that the concentration limits have been set applying the "As Low As Reasonably Achievable (ALARA)" principle although lower risk-based concentration limits have been derived. It appears that since the technical and economic feasibility of reaching the risk-based limits is unknown, these limits have been set to ensure that 75% of inks could comply with the limit (as a percent signifying technical achievability), according to available information. In contrast, the proposed concentration limit for arsenic is solely based on the risk assessment resulting in a very low limit. The Dossier Submitter in this case considered the detection limit of available analytical methods but did not specifically consider the technical feasibility of achieving such low concentrations in tattoo inks. Public Consultation comments state that the proposed limit for arsenic is not technically feasible and instead a concentration limit of 2 ppm is proposed [PC #1905; PC #1928; PC #1931].

In the Public Consultation industry expressed its concern regarding the feasibility of lowering the concentration limits for some heavy metals from the ResAP limits due to fluctuations in their concentration in raw materials [PC #1883; PC #1931]. Specifically, the proposed limits for chromium and lead (when pigment black CI 77266 is used) were considered technically infeasible and instead a concentration limit of 2 ppm is proposed [PC # 1893; PC #1928; PC #1931]. However, the comments did not specify whether other black pigments faced the same issues. Comments by industry were also received on the proposed limit for skin irritant/corrosive and eye irritant/damaging substances as this may restrict detergents and surfactants currently used in tattoo inks for ink dispersal [PC# 1928], although no specific substances were mentioned that could not be substituted.

The Forum expresses a preference for RO2 partly based on the argument that specified limit values are easier to enforce than a 'shall not contain' requirement that is part of RO1. According to Forum, this could also jeopardise harmonised enforcement as laboratories in various Member States could apply different analytical methods and limits of detection. This latter issue could be resolved with harmonisation of analytical methods.

Based on the information from the Background Document, the Forum advice and information from the Public Consultation, RAC has proposed a modification of RO1 concentration limits. RAC considers some concentration limits in RO1 and RO2 are not protective enough. Furthermore the 'shall not contain' provisions in RO1 are considered more difficult to enforce than a specific concentration limit (also confirmed by Forum) and for some substances practical considerations were taken into account. SEAC concurs with the approach followed by RAC to arrive at modified concentration limits for RO1 and SEAC supports these limits.

SEAC considers that, while concentration limits are set on a sensible rationale, information in the Background Document on whether the proposed limits are technically and economically feasible for all substances in the scope of RO1 and RO2 is limited. SEAC concurs with the Dossier Submitter's argument that concentration limits higher or equal to the CoE ResAP(2008)1 (such as proposed for chromium) are in theory technically and economically feasible because of proven level of compliance with ResAP. The proposed limit for lead in the amended RO1 appears feasible for most of the black inks on the market (NVWA 2017) and can act as alternatives to pigment black CI 77266. The Public Consultation did not provide information why other black pigments are not suitable as alternatives for pigment black CI 77266. The proposed limit for arsenic in the RAC modified RO1 appears to be technically feasible for at least white pigments with the highest grade of purity [PC #1905]. No information has been received on its economic feasibility. Concerning the proposed limit for irritant or corrosive/eye damaging substances, SEAC concurs with the Dossier Submitter's assumption that alternatives without harmonised classifications in the scope of this proposal would be available.

Further information on the feasibility of the RAC modified concentration limits was gathered in the Public Consultation of the SEAC Draft Opinion. The following responses were received:

- One stakeholder challenged technical feasibility for pigment black CI 77266 of the RAC modified concentration limit for lead of 0.00007 % (w/w). Oil based pure pigments they use contain between 2.6 and 6.5 ppm which are formulated at 25% in tattoo inks. SEAC considers that taking into account stated maximum pigment concentration of 25% the lower limit of lead in analysed batches (2.6 ppm) would result in 0.000065% of lead in ink, which is below the proposed concentration limit of 0.00007%. Based on this information SEAC concludes it is possible to obtain low level of lead in pigment black CI 77266, although it may be challenging for industry;

- One stakeholder requested a nickel concentration limit of 10 ppm instead of 5 ppm as proposed by RAC as it would be hard to achieve for iron oxide pigments. SEAC notes it is well recognised that nickel is a common impurity in inorganic pigments, especially iron oxides. However, in SMPA 2018, although there are samples with high nickel content (up to 61 ppm), there are also some samples of tattoo inks with inorganic red pigment (iron oxides) in which nickel concentration was below 5 ppm, a limit proposed in RAC-modified RO1 (e.g. 3.5 ppm, 2.1 ppm or 4.5 ppm). Therefore, SEAC concurs with the RAC modified concentration limit for nickel as also SEAC considers it technically feasible;
- One stakeholder requested not to support the concentration limits for metal impurities present in black, white, blue/green and red tattoo inks based on the fact that it is not feasible for them to synthesise highly purified pigments and their dependence on pure pigments available on the (cosmetics) market. According to them, RAC modified concentration limits for antimony, arsenic, lead and cobalt are set too low to be technically feasible. SEAC considers that for black inks more information is available in SMPA 2018 () in which no concern was raised for these metals in the majority of 15 analysed black inks up to the limit of quantification which was close to the RAC modified concentration limits. No other information challenging the RAC modified concentration limits for these metal impurities was available. Therefore, SEAC takes note of RAC conclusions on risk on these substances and does not propose further changes to their concentration limits; One stakeholder based on risk considerations challenged the concentration limits for PAAs that are harmonized sensitisers in comparison with non-PAA sensitisers and one stakeholder challenged the concentration limit for Benzo[a]pyrene of 5 ppb. No socio-economic considerations were raised in these comments, therefore, SEAC takes note of RAC conclusions on risk on these substances and does not propose further changes to their concentration limits;
- One stakeholder proposed that eye irritants are excluded from the scope of the proposal and that the concentration limit for skin irritants is increased to 1% w/w, as the limits for eye/skin irritants and corrosives in RAC modified RO1 are not based on risk assessment, which takes the strength and potency of individual compounds into consideration. The stakeholder suggested that there may be future problems with availability of preservatives (please see section on preservatives below), surfactants and pH adjustors with the concentration limits in the RAC modified RO1. SEAC notes RAC's conclusions on the risks from these substances and concludes that there is no sufficient socio-economic information to justify a derogation on the basis of lack of alternative surfactants or pH adjustors.

b) Derogations

The Dossier Submitter proposes to derogate 21 colourants on the basis of the hazards and risks and availability of alternatives (See Supplementary table B in Table 5 of the Background Document). All but one of these pigments were included in the frame of the restriction on the basis of their ban in all cosmetic products under Annex II of the CPR whilst at the same time they are allowed in all cosmetic products without conditions of

use under Annex IV of the CPR.[58] These pigments were placed on Annex II following a group approach based on epidemiological evidence of an increased risk of bladder cancer among women who made regular use of permanent hair dyes over many years. The chemical identity of the permanent hair dyes used in the study is unknown. In response to this finding, the regulatory strategy of the European Commission was to put all hair dye pigments on Annex II unless the cosmetic industry provided information to ensure safe continued use of the specific pigment in the hair dyes application. As stated in the Background Document, tattoo inks do not fall in the scope of the CPR and the tattoo industry was not able to participate in the process even though the CPR Annex II requirements applied to them via national legislation in those Member States that implemented the Council of Europe resolutions. The Dossier Submitter argues that since their risks are not specifically demonstrated, these pigments should be derogated. For one of these 21 pigments, Pigment Blue 15:3,[59] the unavailability of suitable alternatives is also an argument for derogation. Additionally, Pigment Green 7 (not allowed for use in hair colours by Annex II of the CPR and in eye products by Annex IV, column g), is proposed to be derogated on the basis of not being able to demonstrate risk and unavailability of safer suitable alternatives.

The use of and the availability of alternatives for these pigments was tested during the Public Consultation. The comments provided supported the Dossier Submitter's assessment that Pigment Blue 15:3 and Pigment Green 7 are necessary for the tattoo industry to cover this spectrum of colors and no safer and technically adequate alternatives were identified. [PC #1883; PC #1893; PC #1905; PC #1928; PC #1931]. Information for Pigment Blue 15:3 revealed that other blue pigments are lacking in brilliance and change of colour (turn grey) when mixed with white pigments (common practice in tattooing). SEAC has no sufficient information to independently assess the comparative technical performance of the blue pigments. Pigment Green 7 has been largely replaced by its brominated version Pigment Green 36 (which is not in the scope of this restriction as it does not have relevant harmonised classification and is not included in the CPR Annex II or IV). Based on limited hazard information available, RAC concludes Pigment Green 36 cannot be considered a less hazardous alternative to Pigment Green 7. No other alternatives to Pigment Green 7 have been identified to date.

The Public Consultation indicated limited use of the other 19 pigments proposed by the Dossier Submitter to be derogated and for those that are currently used, alternatives are available [PC #1893; PC #1928]. Other stakeholders indicated these pigments are not used in their formulations [PC #1883] or supported the removal of pigments currently not used in tattoo inks from the Supplementary Table B as most of them are not suitable for tattoos [PC #1931].

[58] All 21 pigments are banned in hair colours but allowed in all cosmetic products except Pigment Green 7. The latter is banned in hair colours (under Annex II) and allowed in all cosmetics except eye products according to Annex IV of the CPR.

[59] The discussion on exemption concerns only Pigment Blue 15:3 and not any other crystal modifications of Pigment Blue 15, which is banned in hair dyes via Annex II in CPR (entry #1367).

SEAC notes RAC's opinion that the exemption of the 21 colourants cannot be based on a lack of hazard and risk. RAC concludes this is due to lack of adequate information on their hazard properties and risk for human health.

SEAC finds that there is some socio-economic information to assess a possible derogation of Pigment Blue 15:3 and Pigment Green 7. Some responses in the Public Consultation on the Annex XV dossier made it clear that these pigments are essential for the tattoo industry and safer alternatives with similar technical performance are lacking. This was re-affirmed by three separate comments by pigment manufacturers and one tattoo association in comments received during the public consultation of the SEAC draft opinion. In one of the comments, it was explained that the two pigments together with the closest substitute for Pigment Green 7 (Pigment Green 36) are formulated in 32-69% of the tattoo products marketed by five manufacturers. Furthermore, they provided examples explaining the technical difficulties that would have to be faced if Pigment Green 36 (similar to Pigment Green 7) and Pigment Blue 15:3 would have to be replaced. Finally, they stated a transition period of 2 years at least would be necessary for replacement of 32-69% of all colour tones with the less suitable blue and green pigments. No information was provided on the overall market share of these three pigments of the EEA market. The available information suggests that the shares reported are for tattoo inks primarily manufactured in the US (one of them being a known name on the market, IBIS 2018). JRC 2015b reports that the situation on the tattoo ink market is complex and it is not easy to understand who is producing what and that the majority of tattoo inks on the EU market are imported from the US, which dominates the EU market. SEAC takes notes of all comments received and the opinion of RAC being inconclusive on a derogation due to uncertainties about hazard and risk of Pigment Green 7 and Pigment Blue 15:3 and also on alternatives that may be used by industry for replacement. Taking all information into account SEAC recommends a time-limited derogation of two years for Pigment Green 7 and Pigment Blue 15:3, allowing tattoo ink manufacturers sufficient time to reformulate. SEAC bases this recommendation on the finding that during the public consultations some evidence was provided on the time needed to reformulate,[60] a relatively high percentage of use of these two pigments in tattoo products of five manufacturers, evidence on difficulty to replace the pigments with technically equivalent alternatives and the finding that RAC could not support a derogation pointing at uncertainties about hazards and risks of these two pigments but also on alternatives. SEAC also takes into account RAC's view that alternatives with a more concerning hazard profile are presently used in blue and green inks and its recommendation that further assessment is made of the risks from alternatives by industry and authorities.

[60] Based on information gathered by the Dossier Submitter (interviews and ECHA CfE 2017), it takes between 1 and 3 years to reformulate tattoo inks. The public consultation revealed that the industry has been facing difficulties to replace these pigments with better alternatives and that their efforts are constrained to an extent by no R&D for new pigments in the pigment industry that are suitable for tattoo purposes.

SEAC finds that there is limited socio-economic information and argumentation to support a derogation of the remaining 19 pigments in Supplementary Table B (see Table 5 of the Background Document). SEAC takes note of the fact that the tattoo industry could not participate in the process under the CPR to provide relevant information on safe use to qualify for an exception of inclusion on Annex II for example (according to the provisions in article 15 of the CPR). However, the Public Consultation of this restriction proposal revealed only some of the pigments are used in tattoo inks but all of them can be replaced by alternatives. Furthermore, SEAC takes note of RAC's lack of support for derogating these pigments. As no other socio-economic arguments on the proposed derogations are available, SEAC does not support derogation of the remaining pigments in Supplementary Table B.

SEAC acknowledges that the proposed restriction is structured in a way that any derogation granted on the colourants under consideration will cease in the event of their harmonised classification in Annex VI of CLP for properties in scope of the proposed restriction and considering a dynamic link with Annex VI of CLP will be implemented.

SEAC notes the proposal by the Dossier Submitter to exempt substances classified for carcinogenicity via inhalation exposure only as well as substances that are in gaseous state at ambient temperature as they are not used in tattoo inks and their inclusion in the scope of the restriction would lead to increased testing costs. SEAC notes RAC's support to exempt carcinogens classified only for inhalation route of exposure based on risk considerations. As regards gases, the consultation on the SEAC draft opinion showed that gaseous substances with relevant harmonised classification can be used in tattoo inks as dissolved ingredients at levels above the concentration limits proposed for substances with similar harmonised classifications. Currently the only known gaseous substance with relevant harmonised classification that is used in tattoo inks is formaldehyde. SEAC concludes that the derogation proposed by the Dossier Submitter for gaseous substances with harmonised classifications should be adapted to take into account the above information and limit the concentration of formaldehyde in tattoo inks to that of other CMRs.

c) Labelling requirements

The same labelling requirements are included in RO1 and RO2 in addition to any CLP requirements that also apply to the tattoo ink mixture. SEAC notes that the proposal aims to inform the general public, i.e. consumers have the possibility to receive information on the chemicals in the tattoo ink before they get a tattoo. The Forum advice supports a labelling provision stating "the information handed to the consumer about the tattoo ink, might be the only way to track which tattoo ink that was used, for example if the consumer experiences unwanted health effects after tattooing". To prevent double information (e.g. in case the name of a hazardous substance is already on the CLP label or the instructions for use for the tattoo ink overlap with the CLP precautionary statements) on the label, SEAC supports the alignment of the labelling provision with CLP.

SEAC notes that the labelling provision in RO1, RO2 and RAC/SEAC modified RO1 equally applies to all substances that are "used" (instead of 'present' as in the original Dossier Submitter's proposal) in these inks at concentrations below the proposed limits. This provision intends to generate as much information as possible for consumers undergoing a tattooing procedure without the need for tattoo ink importers or formulators to check for all substances in the scope of the restriction on tattoo inks, including impurities. In other words, the labelling provision applies only to those substances that are intentionally added to the tattoo ink formulation and that are either covered in the scope of the proposed restriction (and used in the ink below the prohibited concentration level) and/or otherwise classified for human health hazards in Annex VI of CLP. SEAC considers the reference to 'use' as advised by Forum an important amendment to make the labelling provisions manageable for tattoo ink formulators. The drawback of this is that the label will not contain information on hazardous impurities present in the ink that are not added intentionally by the formulator. This may reduce the risk management potential of the label for consumers. SEAC notes in general, limited information is available regarding the impact of labelling of tattoo inks on formulator and consumer behaviour. During the public consultation on the SEAC draft opinion one stakeholder requested a complete list of all ingredients to be available for consumers, tattoo artists and physicians. Another stakeholder argued due to the generally small size a tattoo ink package (5-15 ml) the proposed labelling requirements would be challenging and it would not be possible to always use the local language. They requested labelling requirements of the restriction to be aligned with Annex VII of CPR (e.g., to use of well-known CPR symbols). Based on information obtained during the Public Consultations, SEAC concludes that the proposed labelling provision is implementable. SEAC recommends development of specific guidance supporting the implementation of practical labelling requirements for tattoo inks that can be uniformly applied across the EU. SEAC considers additional labelling costs to be a minor fraction of the total estimated €4.4 million incremental substitution costs incurred by downstream users under RO1.

During the opinion making process, two additional labelling requirements were added for nickel and chromium (VI) as these labels are in ResAP but had not been included in the Dossier Submitters proposal. During the public consultation some stakeholders specifically expressed their support for this inclusion. The labels will apply in situations where the substances are in the tattoo ink at concentrations lower than that which would mean the ink is restricted but higher than the limits of detection for these substances.

d) Additional conditions

Colourants in Annex IV of CPR with conditions on their use

SEAC has taken note of the inclusion in the scope of the restriction proposal of colourants included in Annex IV of CPR and RAC's conclusion that a restriction on these colourants in tattoo inks using the CPR specified conditions is justified. SEAC has no socio-economic arguments supporting or questioning the inclusion of these Annex IV colourants in the scope of the restriction, nor did the Public Consultation provide information on this matter.

Restriction on the use by tattoo artists of tattoo inks not meeting the requirements

The restriction covers the placing on the market as well as use of tattoo inks by tattoo artists. A restriction targeting only the placing on the market without obligations for the tattoo artists would be less effective as stockpiled tattoo formulations and concentrated pigments in a tattoo shop would in such case not be covered. Although SEAC notes the dossier contains limited information on the extent to which tattoo artists formulate tattoo inks using pigments in powdered form, SEAC supports this clause to prevent use of non-compliant inks. Furthermore, SEAC notes the assumption by the Forum that inspections will also take place at the premises of professional users of tattoo inks (e.g., tattoo studios, beauty parlours). Possession by tattoo artist of inks or concentrated pigments would direct towards an 'intention to use' and thus, would be enforceable.

Transitional period

The Dossier Submitter has assessed the proposed transitional period against four different elements: availability of alternatives and time required to reformulate tattoo inks, depletion of stocks in the supply chain (including of distributors and tattoo artists), communication in the supply chain and enforcement.

The Dossier Submitter's argumentation is that as the majority of tattoo inks on the EU market are compliant with existing national legislations in those Member States that have implemented the Council of Europe resolutions, industry therefore has knowledge and experience to formulate tattoo inks that are compliant with the proposed restriction. The Dossier Submitter further argues that a transitional period of one year will be sufficient for enforcement authorities to put the necessary systems in place to monitor and enforce the proposed restriction (by building on experience of Member States with national legislation) and to reduce available stocks. Based on this reasoning, the Dossier Submitter expects that the transitional period of 1 year is sufficient to comply with the proposed restriction.

SEAC agrees in principle with the Dossier Submitter's argument. However, with respect to the first argument: high compliance with ResAP, as such this finding does not provide a rationale for a specific 1 year transitional period as proposed. In fact, SEAC notes a generally high level of compliance could point to an even shorter transitional period. On the other hand, SEAC sees that there will be a need for some formulators to reformulate their products, which takes time. The Public Consultation indicated the need for a longer transitional period of 4 or 5 years [PC #1928; PC #1931]. The 4 year period included a 2-year period for the production of compliant inks and another 2 years for stock depletion in the supply chain [PC #1931]. The claim for a longer transition period was re-affirmed by one manufacturer during the public consultation on the SEAC draft opinion, however no justification was provided. SEAC notes that no further information about R&D and reformulation steps is provided in the Public Consultation to explain or justify the requested transition period. Based on the expiration time for products and average shelf-lives at formulators and resellers, SEAC expects no additional costs for resellers and tattoo artists in case of a 2-year transitional period. A shorter transitional period could have an impact on resellers that have non-compliant inks in stock meaning they would incur some sunk costs. For the reformulation of compliant tattoo inks, SEAC could not verify the Dossier Submitter's expectation that one year would be sufficient nor did the Public Consultation provide sufficient information to justify a different transitional period.

The Background Document contains very limited information on the formulation process and states that colourants can comprise up to 60% of the final formulation of tattoo inks. Those colourants often contain impurities. Many of these colourants are produced by pigment manufacturers for industrial applications where a higher content of impurities is not problematic (although pigments with higher purities are manufactured for food, cosmetics, and medical applications). Although some tattoo ink formulators request purity certificates from their pigment manufacturers, it is not known whether this information is sufficient for the average tattoo ink formulator to know the level of impurities in their raw materials, especially as the level of impurities fluctuates between different batches. The assumed relationship between compliance and the manufacturing process cannot be verified by SEAC; however, SEAC assumes that these practices exist today and notes that the majority of inks currently on the market are compliant with ResAP limits.

The time required for stock depletion is dependent on the average shelf-life and expiration time for unopened and opened products. The limited available information in literature and online does not contradict the Dossier Submitter's assessment that a transitional period of one year is sufficient time for stock depletion of non-compliant ink. During the public consultation on the restriction proposal one comment was submitted that suggested that longer time for depletion of existing stock is required, as manufacturers and resellers carry stock for 6 – 12 months, tattoo artists can use inks for about 12 months after opening. No information is available on any costs associated with retailers, formulators or tattoo artists not being able to deplete stock in time or whether costs would be higher than benefits for human health of having a very short transitional period. Hence, information regarding the time needed to deplete stocks is not available and cannot be used as an argument setting an appropriate transitional period. Inks are only a minor fraction of the PMU/tattooing procedures costs; therefore, the cost of not using some stocks could be low and transferable to consumers.

SEAC also has some concerns regarding the need to harmonise and sometimes develop analytical methods. Some stakeholders also echoed a request for harmonised analytical methods during the public consultation of the SEAC draft opinion. The lack of information in the dossier does not allow a judgement whether a one year transitional period would be sufficient in that respect. On the other hand, it is possible to start enforcement of the proposed restriction while analytical developments are ongoing, as long as enforcement authorities take into account that stakeholders do not have fully harmonised analytical methods available. In the Forum advice on the enforceability of the restriction proposal, the 1 year transitional period is not flagged as a major issue of concern: a representative of an enforcement body of one smaller Member State having no national law on tattoo inks in place expressed concern on the short period for implementation. Another (again a representative of an enforcement body of a smaller Member State without a national legislation) stated that they will be ready within one year. SEAC considers there may be differences between Member States as regards the work that needs to be undertaken to enforce the new restriction. Enforcement bodies in Member States that have not implemented the Council of Europe resolutions would need to build experience. In the Forum advice it is recommended to create a forum for exchange of experience and to update the Compendium of analytical methods for types of substances that have commonly been found in past Member State's enforcement actions. A comment in the Forum advice, however, noted that the restriction can be enforced already on the basis of labelling.

In conclusion, SEAC sees there are some arguments for both a shorter and longer transitional period compared to the 1 year proposed by the Dossier Submitter. No clear socio-economic arguments are available supporting any specific transitional period. A longer transitional period would lead to a delay in potential benefits of the restriction taking effect and reduce potential sunk costs for manufacturers and resellers (e.g., associated with depletion on existing stock, which as explained are expected to be minor and affordable for the supply chain). SEAC considers such reduction of sunk costs is however likely to be considerably lower than any expected human health benefits of the restriction being implemented with less delay. SEAC does not have sufficient information to quantitatively assess how different transitional periods would influence the expected costs and benefits. SEAC considers that alternatives are available for most chemicals that will be banned for use in tattoo inks. Time needed to reformulate and deplete stocks across the board may be expected not to exceed a period of 1 year after entry into force. Hence, SEAC supports the proposed transitional period of 1 year as a reasonable timeframe for implementation.

Preservatives

As tattoo inks are not in scope of the CPR, preservatives used in tattoo formulations fall under the authorisation regime of the BPR. According to the Dossier Submitter, the proposed restriction would not change the obligations under the BPR but would limit the type of preservatives that can be authorised for the use. For example, certain preservatives may be restricted for use in tattoo inks due to their harmonised classification (e.g., formaldehyde, 2-phenoxyethanol, triclosan, 3-iodo-2-propynyl butylcarbamate). During the public consultation of the SEAC draft opinion one

stakeholder requested EU-wide positive listing of preservatives in tattoo inks with reference to Annex V of CPR which lists preservatives allowed in cosmetics as a minimum option. SEAC considers a request for positive listing unfounded and concludes that the proposed restriction does not introduce challenges as regards the link with the BPR (see also section B.3.6.1.3 on the availability of alternatives for preservatives).

e) Linkage with CPR

RO1 proposes a dynamic link between REACH Annex XVII and the CPR Annexes II and IV, which ensures any future updates are reflected in REACH. This option aims to ensure the Annex XVII entry for tattoo inks is up-to-date with the latest relevant developments on substances that are in the scope of Annex II and IV of the CPR. RO2 proposes a static link, ensuring that any new CPR (Annex II and IV) substances are added to the restriction only after specific assessment of their risks to human health when injected intradermally, the availability of alternatives and technical feasibility for achieving the proposed concentration limits (i.e., via a new Annex XV dossier).

SEAC notes that dynamic and static link can in principle be applied to any of the proposed restriction options and therefore, focuses on discussing the approach in principle below. The main differences between dynamic link and static link that are considered by SEAC are summarised in Table 8.

Table 8. Comparison socio-economic aspects of Dynamic and Static link with the Cosmetic Products Regulation

Effect	Dynamic Link	Static Link
Time needed to regulate	REACH Annex XVII tattoo entry will be up-to-date with amendments made in CPR Annexes II and IV. The human health benefits due to reduced exposure to hazardous substances in tattoo inks will be almost immediately realised Limited (and potentially insufficient time) for substitution/reformulation	REACH Annex XVII tattoo entry will be updated only after a tattoo specific assessment. The human health benefits would occur later than in the dynamic link Time will be needed to complete the assessment but the process will be more predictable for industry.
Scientific scrutiny	Annex XVII amendments may lack tattoo use specificity (risk of overregulation) as action is on the basis of use in cosmetics	Annex XVII updates will be targeted to tattoo use and will enable scrutiny of risks, concentration limits and alternatives Group approach is possible similar to the approach in this dossier.
Resources authorities	Less resource intensive as no separate Annex XV dossiers would need to be prepared	Burden on Annex XV dossier development for Member States or Commission/ECHA

All currently proposed restriction options contain a dynamic link between harmonised classifications in CLP and the regulation of substances with such classifications in tattoo inks. No concerns were expressed and no other options were proposed during the public consultation; therefore, SEAC does not evaluate such. The restriction will dynamically take effect for those substances in the future receiving harmonised classification of relevance, i.e., CMRs, skin sensitisers/irritants/corrosives and eye irritants/damaging. SEAC notes RAC's support for this dynamic link with Annex VI of CLP and their conclusion that these substances should not be present in tattoo inks. SEAC considers that this should take precedence over technical and economic feasibility of alternatives, which would not be assessed under the dynamic link. Therefore, SEAC supports the dynamic link on the grounds that it will lead to fast realisation of human health benefits following the grouped approach including establishment of proper concentration limits as in the initial restriction proposal and it is consistent with existing regulatory practices (e.g., REACH Annex XVII entry 28-30 for CMRs category 1A and 1B). SEAC takes note of RAC's conclusions that these substances should not present in tattoo inks.

As regards a dynamic link with CPR, SEAC notes that updating the REACH Annex XVII entry for tattoo inks with CPR Annex II and IV changes would in principle be consistent with the dynamic link that the restriction proposes for future substances with harmonised classifications. Its main advantage would be faster realisation of health benefits due to reduced exposure to these substances in tattoo inks, which is also the reason for RAC's support of dynamic link. Such a dynamic link will also be similar to the link that is in place between REACH and CLP for CMRs cat 1 A and 1 B substances and mixtures supplied to the general public. Currently updates of REACH Annex XVII entry 28-30 prohibiting supply of CMR substances to the general public follows a simplified mechanism. Any changes to the CLP Annex VI as a result of a RAC opinion on harmonised classification proposal and a REACH Committee decision for CMRs 1A and 1B, lead to an amendment of entries 28-30 with a decision in the REACH Committee without scrutiny by RAC and SEAC. This system follows the principle that CMR substances should not be made available to the general public in concentrations above the generic or specific concentration limits as laid down in the CLP Regulation (or the specific Annex VI entry). This amendment of Annex XVII entries 28-30 hence does not require any separate assessment of the level of the maximum allowable concentration, nor does it require an assessment of alternatives. SEAC considers a dynamic link between CPR and REACH could probably take effect in a similar way. However, SEAC recognises that the reason many substances will be included in the CPR is due to their CMR properties and stresses that the dynamic link with the CLP Regulation would take precedence in these cases for the reasons already explained.

SEAC considers as a drawback of a dynamic link the fact that it does not foresee any scientific scrutiny of the use of the newly added substances in the CPR (Annex II or IV with relevant conditions) in tattoo inks based on socio-economic considerations (e.g., availability of alternatives) and does not allow a concentration limit to be applied, specifically for tattoo inks (as the CPR sets requirements for cosmetic products only). As a consequence the tattoo industry could be confronted with unintended consequences (e.g. ban of use in tattoo inks of hard to substitute substances or concentration limits that are not tested for their feasibility). SEAC notes that also in this initial proposal no substance specific assessment on availability of alternatives or feasibility is performed except for an overall conclusion on availability of ResAP compliant tattoo inks based on surveillance results, although it is noted that this reflects the current conditions on the market.

SEAC notes a static link between REACH and CPR (Annex II or IV with relevant conditions) would be more in line with the general restriction process in which authorities have the legal task of initiating restriction proposals in case of unacceptable risks identified at EU level. The downside of such static link would be that it is more resource intensive for authorities and it will be a time consuming process, leading to delay in the realisation of potential health benefits due to reduced exposure. SEAC notes that for the substances currently included in the restriction based on Annex II and Annex IV of the CPR, a group approach is taken for the assessment of their risks and such approach could also prove feasible for future updates of the restriction by member states. In addition, the Dossier Submitter argues the static link could avoid legislative gaps that could arise from a dynamic link. SEAC finds these examples theoretic and not compelling.

SEAC notes RAC's support for a dynamic link with the CPR and concurs that such a link would ensure immediate benefits for human health as new information on hazard and risk becomes available. The dynamic link has some disadvantages, e.g. there will not be any assessment of technical and economic feasibility of alternatives and tattoo ink formulators will have very limited time to transition to any potential alternatives. SEAC notes this impact of the dynamic link could be dampened by introducing transitional periods between the entry into force and entry into effect of each update taking place, although this will not eliminate the requirement for the tattoo industry to track developments under the CPR in order to comply with requirements for the tattoo inks. Furthermore, there would be no assessment of the technical feasibility of concentration limits for their tattoo ink use, rather the applicable limit for cosmetics would be carried forward (although a similar concern can be expressed for the proposed dynamic link with CLP). It is unclear what consequences any future changes to the CPR may have on the tattoo industry.

A static link would have the benefit of assuring risk assessment of (groups of) substances (including technical feasibility of concentration limits) and analysis of alternatives. The main disadvantage would be that for any future changes to the CPR Annex II and IV to apply to the tattoo inks, REACH Annex XVII would need to be amended through a Member State or ECHA (on request of the Commission) proposing an amendment to the restriction. This would result in a time lag for regulating CPR Annex II and IV substances for tattoo ink uses and substantial associated costs incurred by Member States or ECHA for dossier development.[61] Given the large number of possible alternatives to the restricted substances and a number of substances currently used in tattoo inks for which there is no sufficient information on hazard and risk, it is possible, that updates of the proposed restriction may be required regardless of whether static link is established due to the considerable uncertainties associated with what substances may be used in tattoo inks in the future if their risks are not addressed under the CLP or if dynamic link with the CLP is not implemented.

Taking all aspects into consideration, SEAC has a slight preference for a static link as it has the advantage of proper regulating chemicals for their use in tattoo inks. Furthermore, it offers scientific scrutiny on the analyses of alternatives and feasibility of concentration limits that are defined specific for the use in tattoo inks. Similar scrutiny would not be foreseen in case of a dynamic link, which could result in the tattoo industry being confronted with unintended consequences (e.g. ban of use in tattoo inks of hard to substitute substances or concentration limits that are not tested for their feasibility). SEAC notes that irrespective the type of link with CPR, future updates of the restriction may be required anyway due to large uncertainties about future use of substances in tattoo inks.

B.3.2. Effectiveness in reducing the identified risks

Justification for the opinion of RAC

B.3.2.1. Summary of proposal:

The Dossier Submitter demonstrates that the proposed restriction is targeted at those substances that present risks to human health, through intradermal exposure. By introducing concentration limits to hazardous substances that can be found in tattoo inks, derived on the basis of (semi-)quantitative assessment and practical limits discouraging intentional use, the proposed restriction will reduce the risks to human health from 2021 – the assumed entry into effect of the proposed restriction.

B.3.2.2. RAC conclusion(s):

RAC agrees with the Dossier Submitter that both proposed restriction options (RO1 and RO2), as well as the option proposed by RAC (RAC modified RO1), are expected to reduce health risks posed by chemicals used in tattoo inks, although their effectiveness cannot be

[61] For example, a proposal developed by ECHA as a minimum would require 1 FTE for a period of 34 months (12 dossier preparation, 14 opinion development, 8 decision making phase), which including some consultancy fees would result in 170 000 Euro total costs for the Dossier Submitter and additional regulatory resources for opinion development and decision making.

quantified.

RAC agrees with the Dossier Submitter that technically feasible and less hazardous alternatives are likely to be available, but refers to the uncertainties stated in Section B.4.

RAC is aware that residual risk will remain with all proposed restriction options, but that it is essential to restrict the use of chemicals known or suspected of being able to induce adverse effects in tattooed population. Residual risk, if shown to be significant, should be, then, dealt with by successive EU-wide measures, primarily through updating the restriction.

RAC considers that regular updates of the restriction proposal are expected to increase restriction's effectiveness.

B.3.2.3. Key elements underpinning the RAC conclusion(s):

As elaborated in section B.1.2.3.3, the main reasons why RAC cannot give a quantitative estimation of risk reduction are stated below.

- For recognised tattoo-related skin effects, both of irritant and allergic nature, and for limited number of systemic effects (e.g. generalised eczema), epidemiological data have too many limitations to provide a reliable estimate of incidence.
- A clear causal link between adverse effect and specific chemical(s) in tattoo ink is possible to establish only in limited number of cases.
- There are uncertainties related to other adverse effects (e.g. foreign body reaction) for which pathophysiological mechanisms also involves mechanic tissue injury or tattooing technique (e.g. pigment overload), as well as individual predisposing factors (e.g. degree of fibrous tissue reaction to an injury), which are not expected to be influenced by the proposed restriction.
- It is not known which chemicals will replace restricted substances, and for potential alternatives for which health risks are unknown, the risk reduction capacity cannot be assessed.

The first bullet applies both to tattoo-related minor complaints (e.g., mild swelling, mild itching, light and barely visible keratinisation, or mild and transient phototoxic reactions) and to more severe changes which often require medical attention (e.g., inflammation with more pronounced swelling, reddening and more intense sensitivity of the tattoo, pronounced keratinisation, chronic allergic reactions such as chronic urticaria of protracted photosensitivity reactions, ulcerative changes or systemic allergic reactions such as generalised eczema). However, although these adverse reactions could be clearly causally related to tattooing, the reported prevalence varied markedly between the studies. For example, mild or mainly minor adverse effects were reported in 54% of tattooed study participants in Klügl et al. (2010) study, 27% in Høgsberg et al. (2013) study, and only 3.3% in the study conducted by the Italian National Health Institute (ISS, 2017).

During the Public Consultation it was pointed out that not yet adequately understood decomposition products within the skin could be responsible for adverse health effects (e.g. allergic reactions) following tattooing (comment #1928a). These adverse effects also

cannot be expected to be (fully) avoided by the proposed restriction.

For other chronic effects, such as carcinogenic or reprotoxic, the link to a tattoo procedure is much less clear, but, on the other hand, they are not expected to be easily detected in tattooed population (reasons are discussed in the section B.1.2.3.3). Nevertheless, RAC considers that the risk of carcinogenic, reprotoxic and other systemic effects cannot be excluded, and is expected to be reduced by the proposed restriction.

Comparing three restriction options, RAC considers that the least protective option is RO2, with lesser expected effectiveness compared to RO1 and RAC modified RO1, due to CLs higher than in the other two restriction options. The RAC modified RO1, compared to RO1, proposes higher practical CLs for carcinogenic/mutagenic substances, substances in Annex II and IV (column "g") of the CPR and for arsenic. On the other hand, the RAC modified RO1 is expected to be more protective for local (skin) adverse effects, which are most frequently reported among tattoo-related toxic effects, as well as regarding reprotoxic effects and adverse effects of some impurities (copper, barium, nickel, cobalt). Compared to RO1, the RAC modified RO1 is also expected to be more favourable from the aspect of enforcement.

RAC considers that regular updates of the restriction are very important for improving its effectiveness, since they are expected to allow, among others:

- the risk assessment of colourants and other chemicals used in tattoo inks for which information on hazards and risks are inadequate at the present moment;
- the risk assessment of colourants and other chemicals in future tattoo inks, which were never used before in this application;
- the risk assessment of azo colourant decomposition products by azo bond cleavage;
- assessing of new information on health risks of intradermally applied chemicals, which are generally lacking at the present moment (perhaps leading to different specific concentration limits being needed);
- the risk assessment of chemicals and their degradation products during laser tattoo removal;
- the risk assessment of colourants containing nanoparticles;
- the correction of potential legislative gaps arising from application of dynamic link with the CPR.

RAC therefore recommends to the Commission that ECHA could be given the responsibility to periodically assess the restriction. To support this, Member States could be asked to regularly report tests and enforcement carried out in their territory to the Commission, which then could be passed to ECHA. The practicality of such a measure has not been assessed.

RAC is aware that other measures, such as hygienic requirements as well as registration, certification or training requirements of tattoo artists, are important for the safety of tattooing procedures, as indicated during the Public Consultation. These measures are not in the scope of proposed restriction, but they are under national jurisdiction of the EU Member States. They are expected to increase effectiveness of the proposed restriction.

In addition RAC supports the obligatory use of informed consent before each tattooing

session, which is also expected to increase effectiveness of the proposed restriction. Informed consent should make a consumer more aware of health risks and contraindications related to a tattooing procedure.[62] Among other issues, it should include the information on the risks related to possible presence of traces of skin sensitising and CMR substances in tattoo inks, risks related to sun exposure, potential laser removal and to other adverse health effects that could not be covered by this restriction proposal due to lack of available data (e.g., foreign body reaction), as well as on contraindications for tattooing procedure and proper care of the tattooed skin. According to the survey on the diffusion, characteristics and risk awareness regarding tattooing in Italy (Renzoni et al., 2018), only 39% of tattooed study participants were aware of contraindications, 66% were informed on health risks related to tattooing, and only 51% signed informed consent (although it is obligatory in Italy; JRC, 2016b). Informed consent content and the best option how to regulate it, are suggested to be assessed on a national level or in the restriction review.

RAC considers that the proposed restriction may also give an initiative for industry to develop a new branch of colourants' production dedicated specifically to tattoo inks. This would change the present situation in which the colourants used in tattoo inks are often manufactured for other purposes (e.g., industrial applications such as printer inks or car paints), so they may contain levels of hazardous substances that are not appropriate for injecting into the human skin.

Risk reduction capacity of alternatives

Due to high number of substances that are found or can be used in tattoo inks and high number of substances in the scope, the Dossier Submitter did not investigate the availability of alternatives for each individual substance included in the scope. Instead the Dossier Submitter used, as a proxy, national surveillance results indicating compliance with national legislation or CoE ResAPs recommendations. The Dossier Submitter concluded that there are tattoo inks currently on the market that are compliant with CoE ResAPs recommendations and with national regulations in several EU Member States, indicating the availability of alternatives (potentially with the exception of for two pigments, Pigment Blue 15:3 and Pigment Green 7). This conclusion is supported by the results from the Danish Competent Authority survey in 2012 on tattoo inks used in Denmark which showed that there are inks on the market in all colours that meet CoE ResAP(2008)1 (DEPA, 2012a; Background Document section B.2.3). Since for a great majority of substances the concentration limits in restriction options proposed by the Dossier Submitter (RO1 and RO2) and by RAC (RAC modified RO1) are similar or higher

[62] This is partially covered by point 8 in the restriction text ("The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing this procedure"). Nevertheless, although information on the label should be made available to a consumer, it does not obligate a consumer to read it. Signing puts more weight on awareness (it could be expected that people will read the warning if they have to sign the document). Further, it is questionable how many consumers will understand implications of the labelling, e.g., translate labelling warning to potential contraindications. In addition, there are contraindications (e.g., diabetes, anticoagulant therapy) which are not related to chemicals in a tattoo ink, but to tattoo procedure as such.

than those enforced by Member State national legislation based on the CoE ResAP recommendations, the Dossier Submitter expects that a higher proportion of tattoo inks currently on the EEA market will meet the proposed requirements.

RAC agrees with the Dossier Submitter's approach, since it considers that individual substance assessment is not feasible considering the high number of substances in question. In addition, for a large number of substances that potentially could serve as alternatives, it is not realistic to explore their hazard and risk profiles.

Regarding specific groups of substances according to their function in tattoo inks (colourants, auxiliary ingredients, impurities), RAC considers that for colourants *per se* (i.e. not taking into account colourant impurities), less hazardous alternatives are available (potentially with the exception of Pigment Blue 15:3 and Pigment Green 7). Public Consultation comments (comments #1883, #1905) and information on surveillance of currently available tattoo inks that meet the requirements of the CoE resolutions support this conclusion. However, it is uncertain what new pigments will be used in the future and whether their hazards and risks are sufficiently investigated.

However, a concern was raised during the Public Consultation that CLs proposed by the Dossier Submitter for some impurities, especially arsenic, chromium (VI) and lead, could be too low to be technically achievable (comments #1893, #1905, #1928, #1931).

- For arsenic, information for the range of values in colourants, including high purity substances, was provided. RAC proposed a practical concentration limit (0.00005%) higher than that proposed by the Dossier Submitter, which is in the range of values found in tattoo colourants (0.000013% to 0.006%, according to Public Consultation comment #1905 and 0.000002% to 0.006% w/w according to JRC 2015b in 1 165 samples). Although another comment warned that even CL of 0.00004% might be too low for iron oxides (comment #1928b), no further information (e.g. on range of arsenic concentrations in iron colourants or feasibility of alternatives) were provided.
- For chromium (VI), a higher concentration limit was proposed: several public consultation comments (#1893, #1912, #1931) mention that the CL of 0.00002% proposed by the Dossier Submitter and as set in CoE ResAP(2008)1 is too low. A limit of 0.0002% instead was proposed. However, insufficient information has been submitted for assessing the proposed concentration limit (e.g. no information on range of values found in tattoo inks or technical reasons which prevent compliance with 0.00002% w/w[63]). RAC, therefore, proposes a CL of 0.00005% w/w in line with the limit for other carcinogenic and mutagenic substances.
- Regarding lead, a concern was expressed for technical achievability of the proposed

[63] The concentration limit proposed by the Dossier Submitter for chromium (VI) (0.00002%) is the same as in the CoE ResAP(2008)1, and, as the Dossier Submitter pointed out in their reply to this comment, "it is not clear therefore how companies have been complying with the Member States legislation based on that measure".

CL (0.00007%) in two public consultation comments (#1893, #1931). One comment spoke of the presence of lead as an impurity in Pigment black CI 77266 (carbon black) and a CL of 0.0002% was proposed instead. It was explained that this colourant is manufactured from oil, that the concentration of lead varies between 0.00026% and 0.00065% in the pure pigment, and that "it is not always possible to get pigment with low concentration of lead" (i.e. less than 0.00028%). Nevertheless, in the Swedish report[64] lead in this colourant (two samples) was below LoQ of 0.0001%, and Danish EPA survey (DEPA, 2012a) showed that the limit of 0.00007% is achievable for all colours tested. JRC 2015b reported that the concentration of lead in 2 175 samples ranged from 0.0000015% to 0.04015% w/w. In addition, as the Dossier Submitter pointed out in their reply to the comments, it was not specified what would be the impacts if this colourant cannot be used. RAC, therefore, supports the CL proposed by the Dossier Submitter.

Another concern raised during the Public Consultation relates to surfactants or dispersing agents, as auxiliary ingredients (comment #1928). It was stressed that "a limit of 0.1% surfactants which are often irritants would make a good ink dispersion nearly impossible. Especially light fast pigments that are more stable and thus preferred in terms of toxic properties are more complex to disperse". However, no further information on this group of substances (e.g. which are the most commonly used chemicals as surfactants/dispersing agents in tattoo inks and a concentration needed to ensure their function, availability of potential alternatives) were provided during the Public Consultation. RAC, therefore, cannot further assess this concern. This could be further assessed during the Public Consultation on the SEAC draft final opinion.

Regarding preservatives as auxiliary ingredients, which are frequently skin sensitising and/or skin irritant, there are indications that safer alternatives exists. The Dossier Submitter considers that numerous alternatives exist, since Annex V of the CPR contains almost 150 preservatives allowed in cosmetic products (although no data are provided on how many of those are technically feasible as alternatives). Several preservatives are currently approved under the BPR which may be used in biocidal products used to preserve tattoo inks. It is unknown currently if biocidal products are authorised in Member States under the BPR for this use. In addition, as stated in the Background Document (section D.2.1), Norway has a positive list of 26 preservatives with low sensitisation potential. During the Public Consultation, concern regarding availability of safe alternatives for preservatives was not raised.

The main uncertainties regarding availability of alternatives are related to the facts that:

- the scope of the proposed restriction is somewhat wider than the scope of CoE ResAPs and national legislations based on them (e.g. CoE ResAPs do not include some skin sensitisers, skin corrosives or irritants or serious eye damage or irritant

[64] Swedish Medical Products Agency (SMPA) report 2018-04-23: Kontroll av tatueringsfärger för tatuering och permanent makeup

substances as groups of substances with harmonised classification);[65] and
- concentration limits proposed by RAC for cobalt, antimony and organometallic tin are lower than those proposed by the Dossier Submitter or recommended by CoE ResAP(2008)1, and could not (yet) be discussed in the Public Consultation. For justification of concentration limits proposed by RAC for these elements, please see Appendix 4 (section *Remaining substances on Table 3 of the CoE ResAP(2008)1*).

Nevertheless, despite these uncertainties, less hazardous alternatives are, generally, expected to be available, since there are significant similarities between the proposed restriction and CoE ResAPs recommendations, already incorporated into national legislation in several EU Member States. Remaining uncertainties (primarily related to surfactants and other irritants and skin sensitisers, as well as some metal impurities) are proposed to be dealt with during forthcoming Public Consultation, and, if needed, further examined in any review of the restriction.

B.3.3. Socio-economic impact

Justification for the opinion of SEAC

B.3.3.1. Costs

B.3.3.1.1. Summary of proposal:

The Dossier Submitter estimates that the incremental substitution costs for downstream users of tattoo ink and PMU as a result of RO1 will likely be low as technically feasible alternatives with similar or better hazard and risk profiles exist. For those colourants where alternatives have not yet been identified, a derogation is proposed. The majority of tattoo inks currently on the market meet the ResAP recommendations and requirements of national regulation in several Member States. As both restriction options (RO1 and RO2) propose concentration limits that are similar or higher than those enforced at national level, it is expected that a high proportion of tattoo inks and PMU currently on the EU market will meet the proposed requirements.

Therefore, the incremental substitution costs are estimated at about €4.4 million annually during the temporal scope of the analysis (in 2016 values) for EEA31 (European Economic Area). As RO2 imposes less strict requirements than ResAP and RO1, it is anticipated that more tattoo inks and PMU on the market are already compliant with RO2. Therefore, the substitution costs for RO2 would likely be lower than those estimated for RO1. Incremental enforcement (analytical testing and administrative) costs to be incurred over the temporal scope of the analysis are estimated at €235 000 annually.

[65] In effect, this restricts 17 additional substances for which there is information on presence in tattoo inks in comparison to the CoE resolutions.

B.3.3.1.2. SEAC conclusion(s):

SEAC agrees with the methodology used by the Dossier Submitter to assess the cost of the proposed restriction. However, due to lack of information, several assumptions regarding key parameters were made by the Dossier Submitter. Overall, SEAC agrees that the proposed estimate provides an indication of the order of magnitude of the costs, with possible underestimation due to using incidence as a proxy, and to the design of the "high volumes" scenario.

B.3.3.1.3. Key elements underpinning the SEAC conclusion(s):

SEAC agrees that the geographical boundary for the calculations (the EEA 31) is appropriate.

Substitution costs

Review of the methodology to estimate the substitution costs

To estimate the substitution costs, the Dossier Submitter multiplied the annual amounts of non-compliant inks that would be placed on the market in the absence of a restriction (2012-2040) by the unit substitution costs of the inks:

$$Substitution\ cost\ Year\ N = (Volume\ put\ on\ market\ Year\ N)\ \text{x}\ (Share\ of\ non-compliant\ inks)\ \text{x}(Price\ difference)$$

Then a Net Present Value (and an annualised value) of the substitution costs for the period 2021-2040, in 2016 values, were calculated using a discount rate of 4%.

Therefore, substitution costs depend on

1) the annual volumes of non-compliant inks (themselves computed as annual volumes of inks put on the market multiplied by the share of non-compliant inks)
2) unit substitution costs

For the current 2016 volumes of ink, the principle followed by the Dossier Submitter is to multiply the current number of tattooists in the EU by the estimated average volume of tattoo ink used currently by each tattooist on an annual basis (JRC 2015b, stakeholder info). Then the future annual volumes placed on the market are, for future year N, estimated as the 2016 volumes corrected by the ratio of tattoo incidences between year N and 2016:

$$Volume\ put\ on\ market\ Year\ N = (Volume\ put\ on\ market\ 2016)\ \text{x}\left(\frac{incidence\ Year\ N}{incidence\ Year\ 2016}\right)$$

This is a simplification, since the annual volumes are also dependant among others, on the number of tattoos per person per year, size and style of tattoos. SEAC agrees that, due to the lack of data, how these parameters change in the future is unknown, and that they cannot be taken into account in the calculation of tattoo ink volumes. Using incidence could lead to underestimation of future volumes over the study period because it does not take explicitly into account inks used for people already having at least one tattoo. In order to provide an idea of the sensitivity of using incidence as a proxy, SEAC also used prevalence (therefore tending in this case to overestimate volumes, because of the underlying assumption that every tattooed individual will continue getting more tattoos annually for the rest of their life) and found that volumes in 2040 in the Main scenario would then be double those projected using the ratio of incidences.

SEAC concludes that it is acceptable to base an indicative assessment of the future volumes on the incidence of getting tattooed for the first time, but keeping in mind it could underestimate future volumes.

This incidence of people getting tattooed for the first time of 0.53% at the beginning over the study period (2015-2042) is estimated based on the past period 2003-2014, using information on population (from Eurostat) and prevalence in 2003 (6%)[66] and 2014 (12.1%) (JRC 2015b). The Dossier Submitter made, using assumptions, three scenarios for future incidence rates (Low, Main, and High), that are used to derive three (Low, Main, and High volume) scenarios for the volumes of tattoo inks placed on the market annually.

Table 9. Incidence rate scenarios

Incidence	2015-2025	2025-2030	2030-2042
Low	0.53%	0.27%	0.13%
Main	0.53%	0.53%	0.53%
High	0.80%	0.53%	0.53%
Legend:			
Calculated			
Scenario			

[66] The value of 6% for 2003 adopted by the Dossiers Submitter is a mean between 4 and 8% values that are reported *in JRC, 2015b. Safety of tattoos and permanent make-up – State of play and trends in tattoo practices, Report on Work Package 2, s.l.: European Commission Joint Research Centre.* This JRC report adapted existing information for tattooed and pierced population to tattooed-only population from the prevalence for tatooed and pierced population (5 to 10% in 2003) reported in a DG SANCO 2003 Document "Recommendations for regulatory action in the EU on the safety of tattoos, body piercing and of related practices in the EU".

In terms of prevalence of tattooing in the EEA population, the above incidence assumptions give the following results:

Table 10. Prevalence scenarios

Prevalence	2014	2016	2021	2040
Low	12.10%		15.70%	20.30%
Main	12.10%	13.10%	16.20%	26.10%
High	12.10%		17.50%	28.50%

Legend:

JRC study

Derived using incidence assumptions and EuroStat population projections

The Dossier Submitter highlighted the uncertainty in projecting fashion trends and, based on consultations with formulators and tattoo artists, considered that the future trends of tattooing could be similar to the way fashion evolves over time, and that after a period of growth, it could probably progressively become out of fashion under the Low scenario, or stabilise under the Main incidence scenario. SEAC finds the Main and Low incidence scenario are plausible but only illustrative since long-term projection of fashion and cultural trends is inherently uncertain. However, SEAC has reservations regarding the consistency of the High scenario, where incidence would return back to levels assumed under the Main scenario after 2025. This leads to prevalence in 2040 only slightly higher than the Main scenario (28.5% versus 26.1%). SEAC agrees that this is a possibility but finds that to get a broader view of the impact on the conclusions of assumptions for different future scenarios, a High scenario in which incidence is continuously growing could have been more informative. A High scenario where an incidence of 0.8% is assumed for the remainder of the study period will result in a prevalence of 32.5%. Therefore, SEAC overall agrees with the future projections, but finds they are uncertain, more to be understood as being illustrative of possible future situations than predictive, and that their upper range could be underestimated.

In terms of uncertainties of projected volumes, SEAC also notes that given that no information from stakeholders has pointed otherwise, an assumption is made that to get to the same effects (in terms of aesthetics, longevity, etc.) the same volume of a compliant ink compared to a non-compliant ink has to be used. SEAC agrees with this assumption.

A key assumption of the substitution costs assessment is that they can be approximated with the price difference between compliant and non-compliant inks. The price difference is set by a) the (constant) price for non-compliant inks, and b) an assumption of the relative price difference in percent. The price difference is assumed to be constant over the study period. This assumption tends to overestimate the substitution costs, since it could be expected that, with the increasing market for compliant inks, the price could decrease in the future due to economies of scale (considering no major supply problem).

SEAC notes that the Dossier Submitter uses a mean value of the price, but notes that this price is very variable (between €6 and €25 per 30 ml for tattoo inks) and using a mean value introduces uncertainty. SEAC finds that the price estimation is based on a reliable dataset, however with the observation that it was difficult to check with the information available whether the prices reported by the JRC reports are only for non-compliant inks.

Regarding the relative price difference, the Dossier Submitter assumes in the Main scenario that conforming inks are 15% (High scenario 30%) more expensive for tattoo inks, and 20% (High scenario 40%) for PMU inks. The price difference between compliant and non-compliant inks comes from interviews with a total of seven manufacturers[67], from the call for evidence (one answer by a manufacturer), from surveys of tattoo artists and reports by the JRC. The information provided varies from 0% to 40% for tattoo inks and from 0% to 70% for PMU inks. Given the low response rate to surveys by the Dossier Submitter, SEAC considers that the chosen figures for price difference are acceptable but uncertain (large contrast between estimates from different information sources). No additional information was received during the Public Consultation on the dossier.

For the share of non-compliant tattoo inks, the Dossier Submitter used a constant value over the study period, with 3 possible scenarios: 30%, 50% and 70% for tattoo inks. For PMU inks, the assumptions are respectively 0, 10% and 20%. These values are combined with the three Low, Main, High scenarios for the volumes of inks put on the market, in the following way, to provide a set of 9 values for the total substitution costs:

Table 11. Total annualised substitution costs for 2016 estimated by the Dossier Submitter (in euro)

	Non compliance scenario	**Tattoo : 30% PMU : 0%**	**Tattoo : 50% PMU : 10%**	**Tattoo : 70% PMU : 30%**
Volumes scenario				
Low		1 177 471	2 806 428	4 435 385
Main		2 095 694	4 353 847	6 612 000
High		2 437 107	4 939 207	7 441 308

[67] For confidentiality reasons, SEAC could not have access to the information provided in each interview.

The 30% - 70% range reflects the range of non-conformity reported for tattoo inks in market surveys analysed by the Dossier Submitter (with actual range from 15% to 70% non-compliance with chemical requirements). In the Main scenario, the Dossier Submitter used a non-compliance for tattoo inks of 50%, but indicated that this non-compliance rate is conservative. SEAC agrees that the information available from surveys carried out in several countries in the EEA (Germany, Italy, Sweden, and Switzerland) indicate in general of lower non-compliance rate (mean around 35% across available studies), and that non-compliance is expected to decrease with time. The observed non-conformity rates are based on the legislation that was in place where and when the surveys were carried out. These legislations were based on CoE ResAP (different versions) which are similar to the proposed restriction. SEAC however finds that the adequate non-conformity range depends on the specific restriction option because different concentration limits could lead to different non-conformity ranges. While SEAC can draw a parallel to ResAP compliance rates and these expected for the DS and RAC proposed restriction options on the basis of similarities of concentration limits, it notes the possible differences with (RAC modified) RO1 where the limits for some impurities are stricter. Overall, SEAC agrees to use the non-conformity rates in the Main scenario (50% and 10% for tattoo inks and PMU inks respectively) but does not consider it a conservative assumption that would overestimate the costs (given the level of non-compliance in Member States with national legislation). SEAC thus agrees overall with the estimates presented by the Dossier Submitter.

Difference between RO1, RO2 and RAC modified RO1 in terms of substitution costs

The Dossier Submitter could not quantify the differences in substitution costs between RO1 and RO2 arising from the different concentration limits and the different mechanisms to update the scope of the proposed restriction in the future. SEAC agrees that the available information does not appear to enable a quantitative distinction between the two options in terms of substitution costs. Since concentration limits are less stringent in RO2, it can be assumed that more tattoo inks would meet these requirements and that fewer tattoo inks would require reformulation. This would mean lower substitution costs under RO2 compared to RO1. Given the lack of information on technical and economic constraints to manufacture tattoo inks, no quantitative assessment is possible.

It is also difficult, for similar reasons, for SEAC to quantify the differences in substitution costs between RAC modified RO1 and RO1 or RO2. Overall, the RAC modified RO1 has lower limits in comparison to RO2, therefore, it can be expected that it would lead to the reformulation of more tattoo inks in comparison to RO2. The RAC modified RO1 has some higher concentration limits (e.g. for CMRs) but lower for other (e.g. nickel, cobalt) in comparison to RO1 as proposed by the DS with the overall effect on costs being unclear.

The difference in the mechanism to update the future scope of the proposed restriction has unpredictable effects in terms of substitution costs difference between RO1, RO2 and the RAC modified RO1.

Availability of alternatives

SEAC agrees that the fact that there are already compliant inks with the legislation in several Member States is a strong indicator that there are alternatives available. This was also the conclusion of a survey made by the Danish authorities. Also, in response to ECHA's Call for Evidence, no company claimed that there were no alternatives available (other than for Pigment Blue 15:3 and Pigment Green 7 that are proposed to be derogated). This was echoed in the comments in the Public Consultation.

There is a significant level of non-compliance in the Member States having a legislation based on ResAP, and this could be indeed a consequence of lack of EU-wide legislation (as well as counterfeiting), but also implies an uncertainty in the availability of alternatives to all supply chains, because in some cases non-compliance could also be due to the inability to source raw materials meeting the proposed requirements.

An important particular case is that of preservatives, that have the function to ensure the microbiological safety of inks. From the information gathered by the Dossier Submitter it appears that only a small fraction of the preservatives listed in the CPR or actually found in tattoo inks during surveys, would be under the scope of the proposed restriction. The Dossier Submitter concludes from that information that there are many available alternatives for the few preservatives impacted by the proposed restriction. SEAC tends to agree with this conclusion, although the Dossier Submitter did not include information on technical performance requirements and constraints of using preservatives in inks. No information was received during the Public Consultation to indicate that the proposed restriction would limit the availability of suitable preservatives.

Enforcement costs

For all cost components, the annual cost is first calculated by the Dossier Submitter and then converted to a NPV value over the study period (using a 4% discount rate as for other costs).

Analytical testing costs

For public authorities

The costs for an analytical campaign have been based on past experience, and then annual costs are computed assuming that the analytical campaign occurs every 4.5 years. Only costs for those 22 Member State which do not have national legislation are taken into account in the incremental costs of the proposed restriction. The costs of each campaign are based on 100 samples at €500, for each country. The number of samples has been considered by analogy to the four phthalates restriction (in which it was used as an illustrative assumption by SEAC). The €500 per sample is assumed to cover testing for impurities, aromatic amines and some other substances (CMRs). Given the lack of background technical information, SEAC cannot confirm the €500 figure on a technical basis. SEAC finds this can be considered as an uncertain assumption of the reasonable expense per sample for public authorities.

These estimated analytical testing costs may not reflect all the analytical development costs (costs for harmonising methods and knowledge transfer between Member States, or costs for developing new analytical methods). Given the high number of substances involved and lack of harmonised methods in tattoo inks, it is possible that these costs are not negligible. However, efforts have already started in the EU (with a multi-country initiative) to develop harmonised methods in a concerted way between enforcement authorities.

The way in which, due to absence of information, some concentration limits have been set (see above discussion on substitution costs), also creates an uncertainty regarding analytical testing costs.

SEAC notes that no further information was received during the Public Consultation and agrees to use the estimates provided by the Dossier Submitter. SEAC agrees that given public spending constraints, the actual amount spent by public authorities for analytical costs cannot be dramatically higher than the estimated by the Dossier Submitter. SEAC however underlines that given the lack of information, the estimates should only be taken as an illustrative figure. It is uncertain that the actual budget being necessary for the enforcement of the proposed restriction will be actually spent by MS (because of both exogenous budget constraints, and possibly higher analytical testing costs than expected). This could result in analytical campaigns carried out less frequently and with limited chemical scope, which may have negative impacts on the enforcement and risk reduction capacity of the proposed restriction.

For supply chains

Supply chains will carry out internal testing to ensure conformity of their products. The Dossier Submitter explained that these costs are included in the substitution costs, since the price difference between compliant and non-compliant inks (the basis for estimation of substitution costs) reflects the operational costs, including analytical testing costs that manufacturers have to carry out to comply with ResAP recommendations.

The Dossier Submitter attempted to gather information on the testing costs through interviews and survey of formulators. Limited information was received with answers ranging from €20 000 - €50 000 annually, with some mentioning that they also performed testing prior to ResAP. It is unclear what share of these costs can be assumed to be incremental to the proposed restriction as many formulators already market their products in Member States with national legislation and therefore, already perform tests to ensure compliance. SEAC also noted that, in response to the call for evidence, one German ink manufacturer claimed the proposed restriction would entail significant workload and costs in terms of compliance testing. No further information was received during the Public Consultation.

Furthermore, supply chains will also have to adapt to future harmonised analytical methods that are not currently available and this may also have implication on analytical costs.

Therefore, based on the available information, SEAC concludes that the testing costs may also have higher impact on the supply chain than estimated in the Main substitution cost scenario. It is possible however, that this uncertainty is captured to a certain extent in the Higher price difference scenario presented by the Dossier Submitter, in which some testing costs could be captured in the assumed higher price difference between compliant and non-compliant inks.

Administrative costs

For public authorities

The estimation of administrative costs is based on ECHA study of Member State costs of enforcing restrictions, which was used in several other restriction dossiers. Given the comparatively higher complexity of this restriction (wide scope of substances, high number of small actors that may be difficult to reach, comprehensive labelling requirements), it could be that some Member States allocate more resources to the proposed restriction. SEAC however, also acknowledges that given public spending constraints, this may not be possible. Furthermore, there is already a degree of familiarity with the CoE ResAP requirements and transferrable experience in Member States with national legislation which will facilitate enforcement by public authorities.

SEAC also notes that the Dossier Submitter suggested the creation of an EU-wide registry of inks to strengthen the efficiency of the proposed restriction. The cost of this registry is not included in the impact assessment as it was a suggestion for future consideration. The registry might be important to know how to conduct enforcement, e.g., which substances to target in compliance campaigns, especially in the future when the composition of inks might change due to the proposed restriction or other factors such as changes in customer demand, or innovation in tattooing or ink manufacturing techniques.

SEAC will use in its assessment the approach proposed by the Dossier Submitter (based on a "fixed budget" approach for restrictions) but in the event the restriction is not allocated sufficient administrative enforcement budget, the expected risk reduction and benefits of the proposed restriction may not be fully achieved.

For supply chains

Administrative costs for supply chains are, according to the Dossier Submitter, reflected in the substitution costs in the proposed restriction (estimated on the basis of the price difference between compliant and non-compliant inks). However, this restriction is complex for supply chains: in particular, in terms of scope of substances (with links to CLP, CPR), and requirements for comprehensive labelling of inks. Furthermore, current administrative requirements for supply chains are low in a significant share of the Member States that did not implement CoE resolutions (ResAP(2003)2 and ResAP(2008)1).

SEAC concludes that it cannot be excluded that industry stakeholders could face higher administrative costs than estimated by the Dossier Submitter, but is not able to assess their magnitude. However, this uncertainty could be captured to some extent in the Higher price difference scenario presented by the Dossier Submitter, as higher labour costs (including related to the administration of regulatory requirements), similar to other operational costs, could be captured in the assumed higher price difference.

Difference between RO1, RO2 and RAC modified RO1

As a general observation, SEAC notes that the available information does not allow for a quantitative differentiation of enforcement costs between RO1, RO2 and the RAC modified RO1. Under a strictly "fixed enforcement budget" approach the options would have the same costs for enforcement authorities. However, assuming stricter concentration limits would lead to higher analytical testing and development costs, in the absence of a "fixed enforcement budget" approach, testing costs for enforcement authorities could be expected to be the highest for RO1, followed by RAC modified RO1 and RO2. Testing and administrative costs for industry can be expected to follow a similar pattern.

B.3.3.2. Benefits

B.3.3.2.1. Summary of proposal:

The adverse effects associated with exposure to chemicals in tattoo inks can be grouped in: non-infectious inflammatory (e.g., plaque-like, papulo-nodular, ulcerating, hyperkeratoric, photosensitivity, etc.), systemic, malignant, reproductive and developmental effects. Estimating the true overall incidence and prevalence of health effects is difficult for a number of reasons. Skin complications are better studied, however, even those effects are difficult to estimate due to lack of registry and epidemiological studies among others. On average, it can be estimated, on the basis of surveys of health effects of people with tattoos, that 1.7% of tattooed people develop adverse skin reaction of severity that requires a doctor's consultation.

The Dossier Submitter estimates that the social costs of one case of severe non-infectious inflammatory reaction is approximately €4 350 (lower value) or €14 400 (higher value). This is estimated on the basis of costs for treatment and willingness to pay (WTP) to avoid symptoms such as itching and burning sensations that affect quality of life. For the WTP, a proxy for severe chronic dermatitis is used (ECHA, 2016b), as studies have concluded that sufferers of tattoo reactions experienced reduced quality of life similar to known skin diseases such as psoriasis, pruritus, and eczema, albeit the typical tattooed affected areas are smaller. (Hutton Carlsen & Serup, 2015a)

The per case social costs of mild discomforts (experienced after the initial healing process, e.g., photosensitivity, other mild effects associated with itching, pain, swelling, redness, etc.) are likely lower than the presented severe effects above. However, studies reveal that a large number of tattooed people (as high as 42% of respondents, Hutton Carlsten & Serup, 2014) may experience these effects. The overall social costs of these mild effects are not monetised.

The social costs to avoid other systemic, reproductive, developmental or carcinogenic illnesses would be much higher, as they tend to have long-term health consequences requiring medical treatment and higher willingness to pay to avoid (e.g., the willingness to pay to avoid cancer morbidity is €410 000 in 2012 values (ECHA, 2016b)).

B.3.3.2.2. SEAC conclusion(s):

SEAC notes RAC's conclusion on the relation between the chemical composition of the tattoo inks and the observed adverse effects. SEAC concludes that the proposed restriction would result in benefits to society in terms of avoided cases of mild discomforts (mild swelling, itching, erythema) and non-infectious inflammatory reactions. Due to difficulties assessing the incidence and prevalence of these effects and quantifying the risk reduction capacity of the proposed restriction options, these benefits to society cannot be quantified. However, SEAC considers that the benefits related to severe non-inflammatory effects are rather certain, considering RAC's conclusion that there is enough evidence to demonstrate the risk of local (skin) effects, and since these effects among the tattooed population are very well documented. SEAC also notes that, other effects (carcinogenic, reproductive, developmental, and other systemic) are important on a "per case" basis, but that the relationship with tattoo inks is less firm according to RAC[68].

[68] RAC states the evidence for systemic (except for general eczema) or malignant effects is much less clear compared to that for local (skin) effects. RAC section B.1.2.3.3.

SEAC agrees with the Dossier Submitter's analysis that the health benefits of the proposed restriction cannot be quantified and monetised and finds the approach taken by the Dossier Submitter to focus on skin complications for the quantification of benefits justified and understandable. The estimated social cost of severe non-infectious inflammatory effects considers a lower and higher value of the WTP figures used in the analysis. SEAC agrees with the lower and higher value for the social cost used by the Dossier Submitter, although there are arguments that these values could be an under- as well as an overestimation. SEAC acknowledges that there could be other health benefits, with a higher social cost per case than non-infectious inflammatory effects, from the proposed restriction that cannot be quantified.

B.3.3.2.3. Key elements underpinning the SEAC conclusion(s):

Benefits for human health

SEAC notes that, as confirmed by RAC, the complexity and variability in chemical composition of tattoo inks is associated with a risk of diverse adverse effects but clear epidemiological associations are lacking. The Dossier Submitter gives an extensive overview of the type of adverse health effects that are associated with the tattoo process and of those, which are potentially related to the chemical composition of tattoo inks. SEAC agrees with the Dossier Submitter to focus on chemical-related adverse effects only, as these are affected by the proposed restriction[69]. SEAC notes RAC's conclusion is that chemicals in tattoo inks pose human health risk, i.e., local (skin) effects but also systemic and malignant effects, where the evidence is less clear but risks cannot be excluded on the basis of intrinsic properties of substances (that currently or in the future can be found) in tattoo inks and toxicokinetic data from humans and animals. As noted by RAC, because the incidence and prevalence of these adverse health effects is difficult to assess at the present moment, SEAC concurs with the Dossier Submitter's assessment that the health benefits of the proposal cannot be quantified and monetised (unless a direct valuation study would have been attempted). Instead, individual avoided cases of non-infectious inflammatory effects are monetised by the Dossier Submitter and used in the proportionality assessment in a break-even analysis (see proportionality section below). SEAC finds this approach justified and understandable based on the presented data on tattoo complaints and complications.

For the purpose of the break-even analysis, the Dossier Submitter first assesses the type of treatments available for non-infectious, inflammatory tattoo complications and focusses on the severe complications that need pigment removal. SEAC finds the Dossier Submitter's analyses of treatment options following tattoo complications transparent and justified by recent literature from medical experts in the field of tattoo complications.

The cost of treatment is based on medical costs information from dermatologists specialised in tattoo complications from Belgium, Denmark and Finland. The information consisted of either a total cost estimate for medical treatment and dermatome shaving or more specified treatment types and frequency thereof (General Practitioner consult, dermatologist, topical corticosteroids, shaving aftercare, excision, laser treatment, etc.) with subsequent public sector costs. SEAC reviewed the data provided by the dermatologists and how the Dossier Submitter subsequently assessed the treatments costs. SEAC concludes that the Dossier Submitter has adequately estimated an average treatment cost associated with severe skin tattoo complications. SEAC notes that no follow-up treatment is assumed by the Dossier Submitter, potentially underestimating the treatment costs. Also, treatment costs can deviate considerably from the estimated average depending on country, tattoo size and treatment method. SEAC further notes that the Dossier Submitter assumes treatment is initiated within one year after the start of symptoms and in every case is 100% successful. Therefore, the estimated social cost of one case of severe non-infectious inflammatory reactions could be an underestimation if the time between developing symptoms and treatment is longer than one year or the success rate is lower than 100%.

The Dossier Submitter considers also intangible costs for patients with non-infectious inflammatory-type tattoo complications. SEAC finds it likely that such tattoo complications can cause psychological suffering as the Background Document shows a reduced quality of life in tattoo patients that is similar to known skin diseases such as psoriasis, pruritus and eczema. SEAC notes that two aspects should be considered when using the ECHA WTP figures for severe chronic dermatitis as proxy for tattoo complications (ECHA 2016f); representativeness of the symptoms assessed in the WTP study for skin complications as a result of tattooing and representativeness of the studied population relative to the tattooed population. The lower and higher ECHA reference values for WTP to avoid severe chronic dermatitis are based on studies done with psoriasis and eczema patients (ECHA 2016). The reduction of quality of life is described to be similar between psoriasis and eczema patients and patients with tattoo complications (Hutton Carlsen & Serup, 2015a). SEAC finds that this survey (Hutton Carlsen & Serup, 2015a) confirms that the ECHA WTP values used are representative in terms of symptoms.

A difference between the populations that would potentially be of influence on the WTP is disposable income of population. One factor linked with disposable income is age, i.e., it increases with age. The ECHA WTP values are based on populations with a mean age of 55 years. It is likely that the tattooed population that is potentially at risk for tattoo-related skin complications is younger. In the Hutton Carlsen & Serup survey the mean age among patients with tattoo complications was reported to be 33 years. In general, disposable income is lower for younger age groups (at least for most of the study period, since the age of tattooed population would likely increase in the future under the "high" scenario). Hence, the lower expected average age of the EU tattooed population may be seen as having the consequence of the ECHA WTP figures being an upper bound of society's valuation. However, the fact that a sub-population of the EU would have less financial resources than the overall EU population does not necessarily mean that the overall societal WTP to protect them from a risk should be adjusted to the WTP of that sub-population

Other socio-economic characteristics that influence the WTP (like risk-taking behaviour[70]) could be different between the two populations as well, but SEAC did not find convincing evidence of such an influence.

The Dossier Submitter notes that at least in theory a specific survey to directly assess the WTP to reduce risks from tattoo inks could have been considered. SEAC agrees that such a study would also have been faced with the issue that surveyed individuals could not have been informed in quantitative terms regarding the expected risk reduction of the proposed public intervention, but this does not necessarily impede the production of a range of WTP values (however with possibly large uncertainties). SEAC concurs with the Dossier Submitter's assessment that such a study requires substantial resources to obtain useful results while the impact on reducing the uncertainties in the analysis would be marginal and therefore, understands why a direct assessment of the WTP was not pursued.

Overall, SEAC therefore considers the ECHA WTP values sufficiently representative of the societal WTP to avoid severe tattoo complications.

Furthermore, SEAC notes that, although the break-even analysis focusses on non-infectious inflammatory effects, risks of other types of adverse health effects (systemic, malignant tumours, reproductive and developmental, as well as mild effects occurring after the initial healing (>1 month after tattoo procedure) such as photosensitivity, itching, swelling, etc.) could also be impacted by the proposed restriction. SEAC concurs with the Dossier Submitter that the social costs of the other types of systemic, malignant tumours, reproductive and developmental effects are higher per case than the monetised non-infectious inflammatory effects.

Difference between RO1, RO2 and RAC modified RO1

As a general observation, SEAC notes that the available information does not allow for a quantitative differentiation of health benefits between RO1, RO2 and the RAC modified RO1. SEAC takes note of RAC's considerations of the risk reduction capacity of the three options. Therefore, SEAC concludes that the expected benefits of the RAC modified RO1 and the Dossier Submitter RO1 will be larger due to their higher risk reduction potential in comparison to RO2.

Benefits for the environment

SEAC took into account RAC's confirmation that the potential for release of chemicals to the environment is limited in the context of tattooing and PMU, and that the environmental impact of the proposed restriction is therefore limited, compared to human health issues.

B.3.3.3. Other impacts

B.3.3.3.1. Summary of proposal:

Other impacts that can be expected from the restriction include: social, distributional and wider economic impact. Of these, impacts on SMEs are expected to be the most prominent, as many formulators are small or micro enterprises. However, closures are not expected as any cost increases are expected to be passed on to end consumers.

B.3.3.3.2. SEAC conclusion(s):

SEAC agrees that significant wider economic, social, and distributional impacts are unlikely to occur as a consequence of the proposed restriction.

B.3.3.3.3. Key elements underpinning the SEAC conclusion(s):

The Dossier Submitter examines the wider economic, social, and distributional impacts that the proposed restriction could have on economic actors. The impacts are examined separately for pigment manufacturers, tattoo ink formulators, and tattoo artists, anticipating only small impacts for all the actors.

SEAC considers that the proposed restriction could induce some changes in the sector, such as consolidation among actors (smaller formulators that do not currently have ResAP compliant inks), in order to share and reduce compliance costs. SEAC agrees, however, that it is unlikely that closures would occur, since it is probable for economic actors to pass-on costs to consumers (see discussion on proportionality). SEAC also notes that it is also possible that the proposed restriction lowers the risk perception and hence, increases the confidence of consumers in the safety of tattooing, with a potential positive impact on the price for tattoo services.

B.3.3.4. Overall proportionality to the risk

B.3.3.4.1. Summary of proposal:

The Dossier Submitter has concluded that the restriction is proportionate because it is affordable, it is cost effective, and it requires very few avoided cases to break even:

- The cost of tattoo inks represents a small share of the costs per tattoo (marginal costs of the proposed restriction would be less than €1 per tattoo) and even smaller share of the final price per tattoo (e.g., €80-100 in many Western and Northern European Member States and about half that in some Eastern) or PMU (about €350). The price increase of tattoo inks are expected to be transferred to end consumers, whose demand for tattoo services appears to be inelastic. Therefore, the costs increases as a result of the proposed restriction options would likely not lead to disproportionate costs to economic actors and society as a whole.
- The cost-effectiveness of RO1 is estimated at about €60/litre non-compliant tattoo

ink replaced in EEA31. The cost-effectiveness of RO2 is likely to be higher as substitution costs are expected to be somewhat lower than those estimated for RO1.

- For RO1 to break even, between 320 (calculated using cost of illness (COI) plus higher WTP values) and 1 050 (COI plus lower WTP values) cases of chronic allergic reactions (i.e., requiring surgical removal) need to be avoided on an annual basis. This is between 0.02-0.06% of the estimated number of people getting tattoos for the first time each year (19-63 avoided removals for every 100 000 tattooed people) in EEA22 – the Member States currently without national legislation. It is reasonable to expect that these cases would be avoided as a result of the proposed restriction measure as the estimated average prevalence rate of tattoo complications is 1.7% and not all costs are taken into account. In addition, the removal of tattoos due to an allergic or papulo-nodular reaction is just one group of the health outcomes, as a number of people experience complications that require topical or systemic corticosteroids as well as experience mild ongoing complaints from their tattoos and PMU. This is in addition to the potential (unquantified) contribution of tattoo ink and PMU exposure to carcinogenic, reproductive, developmental and other systemic adverse effects.

B.3.3.4.2. RAC and SEAC conclusion(s):

RAC

RAC considers that although the risk reduction capacity of the proposed restriction cannot be quantified, a decrease in incidence of tattoo-related adverse effects is expected, taking into account the broad scope of the restriction and the proposed CLs.

SEAC

SEAC was not able to quantitatively compare the benefits and costs of the proposed restriction, but concludes that the proposed restriction is likely to be proportionate to the risk because:

i. It will bring significant benefits to society (i.e., avoided adverse skin effects and other health impacts), that are likely to be higher than the compliance costs.
ii. It will not have significant negative economic impacts on supply chains.
iii. It is affordable, because compliance costs are likely to be passed-on to consumers through the price increase of tattoo services, and that this price increase will remain affordable.
iv. The proposed restriction is a grouping approach addressing all substances with similar hazard and risk (to the extent possible given available information on hazards), therefore minimising risks of regrettable substitution. This feature increases the confidence SEAC has that expected risk reduction will be actually realised and that the proposed restriction is proportionate.

SEAC notes that the proposed restriction is only "likely" to be proportionate because of the uncertainty surrounding the fact that benefits actually are higher than costs. This uncertainty is not particularly caused by the absence of quantification of benefits, but by both the uncertainties on the qualitative benefits assessment and the quantitative assessment of costs.

B.3.3.4.3. <u>Key elements underpinning the RAC and SEAC conclusion(s):</u>

RAC

As already stated in section B.1.2.3.3 and B.3.2.3, the available data do not allow any quantification of risk reduction capacity of the proposed restriction. The main reasons include significant uncertainties in the estimation of prevalence and incidence of adverse effects related to exposure to substances in tattoo inks. This is due to limitations in epidemiological data and inadequate knowledge on health risk profile of potential alternatives. In addition to these uncertainties, RAC points out that incidence rate could be especially difficult to assess as adverse tattoo reactions (e.g. allergic skin reactions) could occur months and years after tattoo application (Serup and Hutton Carlsen, 2014), with some reactions becoming chronic (e.g. if the allergen is part of the pigments deposited in the dermis and being slowly but permanently released in the tissue; DEPA, 2017a).

Due to these uncertainties RAC is also unable to give an opinion how reasonable it is to expect that avoided cases of surgically removed tattoos due to skin complications (calculated by the Dossier Submitter for a break-even - low indicator) present 0.04-0.12% of the estimated number of people getting tattoos for the first time each year in the EU.

Regarding a comparison of risk reduction capacity of restriction options (RO1, RO2 and the RAC modified RO1), please see comparison of effectiveness for these three options in section B.3.2.3.

SEAC

SEAC could not base its conclusion on a quantitative comparison of the costs and benefits of the proposed restriction, or on its cost-effectiveness, for the following reasons:

- SEAC agrees with the method to calculate the number of cases of chronic allergic reactions for the break-even analysis, but did not find a way to compare the break-even incidence rate of chronic allergic reactions (0.02-0.06%) to the observed tattoo prevalence in the general population (1.8%). This is because of the complex relation between incidence and prevalence that has not been modelled due primarily to the difficulty to quantitatively estimate baseline risk and the risk reduction capacity of the proposed restriction.
- SEAC could not find a way to interpret the cost-effectiveness of the restriction expressed by the Dossier Submitters as €60 per litre of non-compliant ink removed from the market because there does not seem to be an economic assessment of a similar regulation that could be a point of comparison.

SEAC however could base its conclusion on the following elements:

The proposed restriction is likely to be proportionate:

- The proposed restriction will bring significant benefits to society (avoided health impacts of adverse skin effects and other health impacts), even if their magnitude cannot be assessed.
- SEAC finds that the proposed restriction, also when considering uncertainties regarding its compliance costs, is affordable for consumers. The price increase incurred per PMU or tattoo is low (respectively in the order of magnitude of €4 and €1 per procedure respectively), and demand is quite inelastic to price (as reported in a survey in the US quoted by the Dossier Submitter, in which only 8% of respondents stated that price is an important factor in their decision to get a tattoo). The risk of negative economic impacts for supply chains is low, as discussed in the above section on other impacts, also in particular given the affordability to consumers.
- Furthermore, the risk of increased competition from outside the EU seems very limited: a large share of tattoo inks is currently already imported and consumers are not expected to turn to tattoo artists located outside the EU (more so than currently practiced). No risk of profit losses for the EU economy is therefore to be expected.
- Positive economic impacts for the supply chains are possible, given a potential increased level of confidence of consumers in tattooing practice as a result of the restriction proposal (increase in turnover could create an increase in profits).

Considering the above elements, SEAC was able to compare qualitatively the costs and benefits and found that the proposed restriction will bring health benefits and is not expected to have significant economic impacts, and therefore, concludes that the proposed restriction is likely to be proportionate.

Furthermore, the proposed restriction has the additional benefit of avoiding regrettable substitution. Targeting in a single restriction proposal all classified hazardous chemicals in

inks tends to ensure that no regrettable substitution will take place, even if the actual magnitude of health benefits remains uncertain. Replacement of restricted chemicals by not yet classified chemicals is possible, but industry is likely to use long-term alternatives to avoid substitution costs.

SEAC's conclusions and justifications are valid for the three proposed ROs. As explained in the preceding sections on costs and benefits, because of the uncertainties related to i) the impact on different concentration limits in the three restriction options on compliance costs and ii) the risk reduction capacity and also the magnitude of benefits, it is difficult to quantitatively or qualitatively conclude which of the three options is more proportionate. On the one hand, if the concentration limits are an indication of the difficulty to comply with the restriction option, the costs for RO2 are expected to be lower in comparison to the RAC modified RO1 and RO1 as proposed by the Dossier Submitter. On the other hand, the risk reduction capacity and therefore, the benefits of the restriction options, are likely to be in the same order: with those for RO2 likely to be the lowest, followed by RAC modified RO1 and RO1. Therefore, it is difficult to conclude which restriction option is more proportionate on balance; however, all three options are expected to be proportionate and to lead to low economic impacts on the EEA.

Table 12. Summary of costs and benefits of restriction options

Impact	**Restriction Option 1 (RO1)**	**Restriction Option 2 (RO2)***	**RAC/SEAC modified RO1***
Total Compliance Costs	€4.6 million	Lower than RO1 and RAC/SEAC modified RO1	Possibly similar to RO1 but higher than RO2
- Substitution	€4.4 million	Lower than RO1 and RAC/SEAC modified RO1	Possibly similar to RO1 but higher than RO2
- Enforcement	€0.2 million	Lower than RO1 and RAC/SEAC modified RO1	Possibly similar or lower than RO1 but higher than RO2
Social impacts	Moderate	Similar to RO1	Similar to RO1
Wider economic impacts	Minimal	Similar to RO1	Similar to RO1
Distributional impacts	Minimal	Similar to RO1	Similar to RO1
Risk reduction capacity	It would reduce risks	Possibly lower than RO1 and RAC/SEAC modified RO1	Possibly similar to RO1 but higher than RO2
Benefits	Equivalent to the avoided cases of tattoo adverse effects	Possibly lower than RO1 and RAC/SEAC modified RO1	Possibly similar to RO1 but higher than RO2
Break-even	Fewer than 320 – 1 050 avoided cases of tattoo removal due to non-infectious inflammatory complications	Possibly fewer cases required for break-even than RO1 and RAC/SEAC modified RO1	Similar to RO1 and more cases required for break-even than RO2
Affordability	Affordable	Likely more affordable than RO1 and RAC/SEAC modified RO1	Similar to RO1 but less affordable than RO2

Notes: Qualitative comparison to RO1 of RO2 and RAC/SEAC modified RO1 is based on the assumption that lower concentration limits would require more resources to comply with (therefore, would lead to higher costs) and would lead to higher risk reduction and benefits from the proposed restriction. However, some concentration limits of RO1 are lower while others are higher than RAC/SEAC modified RO1. Furthermore, many of the concentration limits proposed under RAC/SEAC modified RO1 may be similar to the effectively enforced concentration limits under national legislation based on ResAP (e.g., for substances that should not be contained in tattoo inks unless not intentionally added). Therefore, the differences of the impacts of RO1 and the RAC/SEAC modified RO1 are concluded to be smaller than those with RO2.

B.3.3.5. Uncertainties in the proportionality to the risks section

RAC

Uncertainties regarding risk reduction capacity raised by RAC are described in sections B.1.2.3.3, B.3.2.3 and in the section above.

SEAC

Uncertainties related to the costs, benefits, and proportionality to risk of the proposed restriction options are discussed in the preceding section. Some of the uncertainties discussed previously (i.e. projections of tattoo ink volumes) only affect the total substitution costs of the restriction but not the cost per tattoo service, and therefore, have no impacts on SEAC's conclusions on the affordability (cost per tattoo) of the compliance costs imposed by the restriction.

Some other uncertainties related to assumptions used in the estimation of substitution costs (related to price differences especially) as well as administrative and testing costs (see discussion on costs above) could affect in theory the cost per tattoo service and therefore, the conclusions on affordability. However, even if these costs were severely underestimated, sensitivity scenarios demonstrate that the price increase would still remain low compared to the prices of tattoo services. As stated earlier, the price of tattoo services is not a leading criterion for deciding to get a tattoo, therefore, the price increase is expected to be passed on to consumers and the restriction is expected to remain affordable even in those higher costs scenarios.

As discussed above, it is possible that the budget for enforcement (testing, administrative burdens) is insufficient regarding the large scope and complexity of the restriction. The implication could be insufficient testing and administrative oversight by both supply chains and authorities, leading to higher non-compliance than expected, and lower risk reduction than expected in DS assessment. It is difficult to assess the impact on the proportionality to the risk of the restriction, because it depends on the (unknown) significance of the possible underestimation, and of the reactions of supply chains and administrations (whether for instance there would be efficient and rapid sharing of information among Member States for analytical method development, whether supply chains could and would use for a period non-EU-harmonised but still valid analytical methods to check and eventually change raw materials and formulations). Therefore this is regarded by SEAC as the main source of uncertainty in its assessment.

B.3.4. Practicality, incl. enforceability

Justification for the opinion of RAC and SEAC

B.3.4.1. Summary of proposal:

The proposed restriction options are practical because they are implementable, enforceable and manageable:

Implementability

- The proposed restriction options propose similar, and in the case of RO2, slightly less strict than the recommended measures in ResAP, which have been used as a basis for national legislation in seven Member States and two additional EEA

members.

- Surveillance results have shown that the majority of tattoo inks and PMU are in compliance with national legislation (50-70%), which suggests industry's ability to comply with the proposed restriction options.
- The proposed transitional period reflects the industry capability to comply with the proposed restriction options.

Enforceability

- Enforcement of national legislation based on ResAP is already taking place in just under a third of EEA31 Member States.
- Systems are in place (under the General Product Safety Directive) to monitor compliance of CoE resolution and to share information on enforcement actions on dangerous products – RAPEX.
- The dossier provides information on the substances found in tattoo inks that present risk to human health and highlights groups of substances that are considered most problematic. This will enable targeted surveillance at high risk substances, which would contribute to effective, lower cost monitoring.
- Analytical methods exist for all groups of substances in the scope of the proposed restriction options. Harmonisation of the applied analytical methods will be beneficial.
- Information on the limit of detection of the currently used methods has been taken into account in the setting of the concentration limits for individual and groups of substances in the scope of RO1 and RO2.

Manageability

- Given the similarity with existing measures (ResAP, the CPR, and the CLP Regulation) and the stakeholder's raised awareness of the issue, RO1, RO2 and the RAC modified RO1 should be clear and understandable to all the actors involved.
- The level of administrative burden is not expected to be higher than in the Member States with national legislation.
- The current compliance rate suggests that the existing regulations are manageable for industry.

B.3.4.2. RAC and SEAC conclusion(s):

RAC

RAC concludes that the proposed restriction is implementable, enforceable and manageable, taking into account the uncertainties discussed below. RAC further notes that their final restriction proposal (see RAC modified RO1) addresses the comments made by the Forum for exchange of information on enforcement (Forum) to further improve the enforceability of the restriction. This includes the addition of practical concentration limits as Forum consider that set concentration limits (vs complete ban) helps with compliance with the proposed restriction's requirements.

SEAC

Taking into account, among other elements, information in the Background Document, the Public Consultation and the advice given by Forum, SEAC is of the view that the proposed restriction options are practical and enforceable (keeping however in mind uncertainties regarding administrative and testing costs).

SEAC concludes there are no compelling socio-economic arguments favouring either of the restriction options. In its proposal for amended RO1 concentration limits, where information as such was available, RAC accounted for practical considerations of the limits for industry and enforcement authorities. Therefore, it can be concluded that the RAC modified RO1 may be easier to implement, enforce, and manage in comparison to the other two restriction options.

B.3.4.3. Key elements underpinning the RAC and SEAC conclusion(s):

RAC

Implementability

RAC agrees with the Dossier Submitter that the proposed restriction is expected to be implementable, both for industry and enforcement authorities. It builds on the existing industry compliance and Member States enforcement practices of national legislation based on CoE ResAPs in approximately one-third of EEA Member States. The proportion of tattoo inks compliant with national legislations based on CoE ResAPs ranged from 50-70% during the previous 5 years of market surveillance, and according to Danish data, there are inks on the market in all colours that meet CoE ResAP(2008)1 (Danish competent authority survey; DEPA, 2012a; Background Document section B.2.3).

The information explaining why 30-50% of tattoo inks on the EU market were not compliant with national legislations based on CoE ResAPs (e.g., containing impurities at levels higher than recommended by CoE ResAP(2008)1) is not available, and this presents another uncertainty (e.g., regarding the extent of availability of alternatives).

Nevertheless, as already discussed in section B.3.2.3, less hazardous alternatives are, generally, expected to be available, and remaining uncertainties (primarily related to surfactants and other irritants and skin sensitisers, as well as some metal impurities) are proposed to be dealt with during forthcoming Public Consultation.

Regarding the transitional period, RAC acknowledges Public Consultation comments from industry in which longer period was proposed (up to 5 years; comments #1883, #1928, #1931), but considers 1 year transitional period as sufficient for the industry to comply, as suggested by the Dossier Submitter.

Enforceability

RAC considers that the proposed restriction is enforceable, but, in line with the Forum advice, a prerequisite for this is to develop harmonised analytical methods for determining the regulated substances in tattoo inks. RAC agrees with the Dossier Submitter that a good indicator of enforceability is the fact that approximately one-third of EEA countries already enforced national legislation based on CoE ResAPs, and that the Member States

without national legislation could build on the experience of the Member States in which the above mentioned enforcement is already taking place.

Comparing enforceability of restriction options proposed by the Dossier Submitter, RAC agrees with the Forum that CLs under RO1, although more protective, are more difficult to enforce compared to CLs under RO2. Namely, as also discussed by the Dossier Submitter, it is difficult to enforce a restriction without a specific limit value as the default enforcement may be the limit of detection (LoD) which is linked to the performance of the available analytical methods and could differ in Member States.[71]

RO2 is expected to be simpler in its content and format[72] for stakeholders. Namely, since this option proposes a static link with the CPR, it requires less cross-referencing to external resources (other regulations). This option is for this reason, and due to set specific limit values (instead of CLs set to LoDs), the preferred option by Forum.

RAC proposes a modified RO1, primarily considering that CLs for some substances are not protective enough under either RO1 or RO2, and that for other substances more easily enforceable CLs are proposed (primarily taking into account technical achievability), while minimising risk for human health (for detailed justification please see section B.3.1.3).

The Public Consultation raised the concern that the restriction proposal in its present form is complex and difficult to understand (comments #1928, #1929). It was also pointed out that chemical analysis of such a large number of chemicals in the scope, and a lack of standardisation of analytical methods, would be a challenge (comments #1918, #1919, #1928, #1931).

RAC acknowledges these issues. Regarding complexity of the restriction proposal, RAC recommends that a guideline for this restriction is developed by the enforcing authorities identifying among others a priority list of substances for enforcement and indicating appropriate analytical method(s) for their determination in tattoo inks. The Dossier Submitter already provided information on the substances found in tattoo inks that present risk to human health and highlighted the groups of substances that are considered most problematic (section D.7.1 in the Background Document). RAC agrees with the Dossier Submitter's suggestion that Member States, at least during the initial period after the restriction's adoption, focus efforts on these high priority chemicals, while detailed analysis of tattoo inks could be performed occasionally by specialised laboratories. These detailed analyses are expected to help in updating of the priority list.

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[71] The Forum provided following justification: „Specific limit value would be easier to enforce than a totally banned substance. If no limit value is set, non-compliance depends on limit of detection of the available method chosen by the national enforcement authority. Member states use different labs and different labs may have different limits of detection and harmonization in the community could be jeopardized. Also, experience of enforcing restrictions and other legislations where no limit value is set tells us that there is more room for economic operators and potential defendants to question our results if there is no specific limit value."

[72] In RO2 option restricted substance are listed in Tables (A-E) within the restriction proposal, so there is no need to cross-reference to other legislation. However, Forum suggests further simplifying of RO2 text, by merging all restricted substances with their respective concentration limits in one table, apart from the ones with a harmonized classification covered by paragraph 1.

The Dossier Submitter states that analytical methods exist for all groups of substances in the scope of the proposed restriction options, except for azo dyes. Information on the available methods is included in Appendix D.2 of the Background Document. RAC acknowledges that the availability of adequate analytical methods (taking into account appropriate matrix, LoD, availability of standard reference material, complexity of a method etc.) for approximately 4 000 substances in the scope is not feasible to ascertain at this stage. However, it could be expected that a continuous research in the field of analytical chemistry of tattoo inks will provide the answers to this uncertainty (e.g., Katz, 2017; Yakes et al., 2017). RAC considers that it is the responsibility of producers/formulators to develop analytical methods, ensuring their compliance with the legislation.

In the meantime, for the substances suggested by the Dossier Submitter to be included in the priority list,[73] analytical methods are expected to be available (with azo colourants as an exception[74]), although not yet standardised and harmonised.

The availability of harmonised analytical methods is not a requirement for proposing a restriction, as noted by the Dossier Submitter. Nevertheless, the Dossier Submitter, the Forum and RAC recognise the importance of standardisation and harmonisation of analytical methods for enforcement of the proposed restriction. This is supported by the comments received during the Call for evidences (ECHA CfE, 2016a) and the Public Consultation (comments #1918, #1919, #1927, #1928, #1931). RAC notes that according to the Dossier Submitter's information, there is an ongoing multi-country project, involving Denmark, Germany, Switzerland and Italy, on developing analytical methods for the regulated substances in tattoo inks. This project is expected to assist with the enforcement of the proposed restriction as well as with development of compendium of analytical methods, in line with Forum's advice.

During the Public Consultation, several stakeholders (comments #1912, #1921, #1928, #1929) expressed preference for the development of a positive list of pigments to be used in tattoo inks. As pointed out by the Dossier Submitter and in Public Consultation comment #1912, there is no possibility to have such a list in a REACH restriction. Nevertheless, a positive list could be introduced in EU Member States at a national level, as already done in Spain and Norway. Spain, under the national legislation on cosmetics, has a positive list of tattoo inks that can be placed on the market, and Norway has a positive list of 26 preservatives with low sensitisation potential. RAC suggests evaluating the efficiency of these examples, and taking the results of the evaluation into account in any future review of the restriction.

Manageability

[73] PAHs for black and dark inks, PAAs for red inks and its nuances, selected toxic elements commonly found as impurities in variety of tattoo inks.

[74] Chemical analysis of tattoo pigments in general is challenging due to low solubility of the pigments, interferences from other tattoo ink components, sometimes low amount of a pigment in tattoo ink, and limited availability of pigment standards (Katz, 2017). Therefore, LoDs are rather high (Public Consultation comment #1913), and the methods are often used only for qualitative determination (Yakes et al., 2017).

RAC agrees with the Dossier Submitter that 50-70% compliance with national legislation based on CoE ResAPs, which requirements are rather similar to the proposed restriction, indicates that the restriction should be understandable and manageable for industry. Experience in enforcement of above mentioned national legislations indicates that the proposed restriction will be manageable for Member States' Competent Authorities as well.

SEAC

SEAC considers the restriction options to be implementable based on similarity with ResAP recommendations already implemented in national law in seven Member States. Industry's ability to comply with ResAP follows from results of surveillance programmes. SEAC sees there are some arguments for both a shorter as for a longer transitional period compared to 1 year as proposed by the Dossier Submitter. Some stakeholders and one Member State enforcement body argue a 1 year transitional period would be too short to implement the legislation whilst others indicate to be ready in one year. Overall, SEAC agrees with a 1 year transitional period as a reasonable timeframe to implement the restriction (See section B.3.4.5.).

SEAC agrees with the Dossier Submitter that the proposed restriction has a level of similarity with existing measures (CPR, ResAP, CLP). SEAC notes that some stakeholders in the Public Consultation stated that the proposed legislation covering numerous chemicals would be difficult to manage. Convincing arguments underpinning this claim were not available to SEAC and experiences based on implemented national law following ResAP show comparable measures are manageable in practice. Therefore, SEAC concludes positively on the manageability.

Assuming the concentration limits are an indication for the number of reformulations required, it can be expected that less strict limits will lead to fewer required reformulations and therefore, RO2 may be more manageable and easier to implement than the RAC modified RO1 concentration limits and, lastly, RO1.

According to the Forum, the restriction is enforceable if further development of methods for sampling and chemical analysis is undertaken. Due to the high number of substances within the restriction scope, and the lack of available standard methods or reference materials (e.g. for azo pigments as indicated in the Public Consultation) for the quantification of all chemicals present in tattoo inks, methods applicable to other matrices should be considered and modified. Information on best available analytical practices can be shared among all relevant stakeholders (e.g., through the Forum Compendium on analytical methods for the enforcement of restrictions or through an ad hoc guidance document on tattoo inks restriction). There is an ongoing multi-country project (Denmark, Germany, Switzerland, and Italy) on developing analytical methods. Together with the compendium of analytical methods that the advice is referring to, this work will also improve the enforceability of the proposed restriction. The Public Consultation indicated that enforcement of the proposed arsenic limit of RO1 and RO2, may be difficult as the limit of quantification of arsenic in tattooing agents is 0.1 mg/kg (0.00001%) [PC #1911; PC #1924] which is higher than 0.0000008% as proposed by the Dossier Submitter under RO1 and RO2. RAC proposed a practical concentration limit (0.00005%) which is above the reported limit of quantification.

The Forum acknowledges that enforcement of national legislation based on ResAP is already taking place in just under a third of EEA31 Member States and that systems are in place (under the General Product Safety Directive) to monitor compliance of the Council of Europe resolutions and to share information on dangerous products – RAPEX (Rapid alert system for dangerous non-food products) – and for non-compliant products – ICSMS (The Information and Communication System on Market Surveillance).

Forum assessed the enforceability of RO1 and RO2. The RAC modified RO1, developed in response to Forum comments, hazard and risk evaluation, and comments from the Public Consultation on the dossier, was not discussed by Forum. As regards ease of enforceability, the Forum has a preference for RO2 based on the fact that a specific limit value would be easier to enforce than a full ban of a substance ("shall not contain"). According to Forum in the latter case, the non-compliance will depend on the limit of detection (LoD) of the analytical method chosen by the enforcement authority. Furthermore, RO2 has a preferable format since it requires less cross-reference to external resources (other regulations). SEAC notes the preferred format could be applied to any of the recommended options and the final format and specification of the legal placement of Tables A-E containing the substances in scope of the restriction is to be decided by the Commission. As regards the LoD, SEAC notes this is rather flagging a need for harmonisation of sampling and analysis than by definition a reason to favour any of the restriction options, the need for harmonisation applies equally to all three. SEAC notes that in proposing the RAC modified RO1 concentration limits, RAC has taken a risk based approach while also considering information on other practical aspects such as technical feasibility and available analytical methods to the extent such was made available.

B.3.5. Monitorability

Justification for the opinion of RAC and SEAC

B.3.5.1. Summary of proposal:

The implementation of the proposed restriction options can be monitored by:

- Member State surveillance programs and compliance controls, with the continued use of RAPEX.
- Tattoo artists and PMU practitioners who will have the obligation to inject intradermally only compliant inks.
- The introduction of separate, EU-harmonised diagnostic codes for tattoo ink and PMU complications by national health boards to enable tracking of adverse effects.

B.3.5.2. RAC and SEAC conclusion(s):

RAC

RAC considers the proposed restriction to be monitorable.

SEAC

Based on reported existing experience in Member States that have implemented the Council of Europe recommendations and the Forum advice on this aspect SEAC concludes that the proposed restriction options for substances in tattoo inks under REACH are monitorable.

B.3.5.3. Key elements underpinning the RAC and SEAC conclusion(s):

RAC

RAC agrees with the Dossier Submitter that in Member States under national legislation systems are in place to monitor compliance and to share information on dangerous products (via RAPEX).

Regarding the introduction of a separate, EU-harmonised diagnostic codes for tattoo-related adverse effects, RAC points out that, at least at the present moment, there are significant uncertainties regarding exact diagnosing of tattoo-related adverse effects (please see section B.1.2.3.3). Potential role of this measure in monitorability is, therefore, presently questionable.

On the other hand, RAC supports the Dossier Submitter's proposal for EEA-wide registry of the chemical composition of inks, which will assist in the gathering of information supporting further action on tattoo inks in the future.

RAC considers that this restriction will set a tool for monitoring of hazardous chemical substances in tattoo inks and will provide information necessary to improve a control of health risks created by these substances which occur or might occur in tattoo inks.

SEAC

Over a third of EEA31 Member States already monitor compliance of the Council of Europe resolution and share information on non-compliant and dangerous products through RAPEX and ICSMS.

SEAC takes note of the Forum support for the suggestion in the Background Document of the introduction of an EU wide registry of tattoo inks, which, among other information, will gather data on the chemical composition of the mixtures. Such database would facilitate the identification of substances which are considered most problematic.

Monitoring the effectiveness of the proposed restriction in reducing health effects of exposure to chemicals in tattoo inks would be possible with the introduction of EU-harmonised diagnostic codes for tattoo inks complications by national health boards. SEAC acknowledges that systemic effects such as cancers will remain difficult to attribute to such a specific cause as tattooing. The harmonised diagnostics codes will be specifically helpful to report in a consistent way on effects that appear with relatively high incidences such as skin allergic reactions or local irritations and allow for identifying substances that may be responsible for such effects.

B.4. UNCERTAINTIES IN THE EVALUATION OF RAC AND SEAC

RAC

B.4.1. Summary of proposal:

The dossier Submitter has identified several sources of uncertainties and analysed their impact on risk estimation in section 3 of the background document. These uncertainties are linked with estimation of the amount pigment/ink deposited during tattooing (mg/cm^2), application of different tattoo equipment, uptake of pigment and soluble substances, release of impurities from pigments, excretion of pigments, soluble substances and impurities. Some of the uncertainties in the risk assessment are related to the limited data available on dose-response relationship used for estimation of risk. There are also uncertainties regarding the appropriate methodology for assessing risks due to intradermal exposure and risks arising from mixtures. The number of substances included in the scope that have actually been used in tattoo inks is unknown. A restriction would therefore likely cover various hazardous substances that could never find use in tattoo inks, however including them in the scope will prevent their intentional and unintentional presence in tattoo inks.

B.4.2. RAC conclusion(s):

Several sources of uncertainty have been identified regarding the assessment of risk, effectiveness and practicality aspects. Nevertheless, RAC considers that these uncertainties are not obstacles for implementation of the proposed restriction, but, on the contrary, could act as an important initiative for scientific and regulatory community to fill existing knowledge gaps.

B.4.3. Key elements underpinning the RAC conclusion(s):

The uncertainties are discussed by the Dossier Submitter in the Background Document (Annex E), and by RAC in sections B.1.2.4, B.3.2.3, B.3.3.4.3, and B.3.4.3. The most important issues are summarised below.

The uncertainties related to exposure scenario, hazard and risk assessment are primarily due to inadequately explored intradermal route of exposure to chemicals. Limited data are available for toxicokinetics of intradermally injected substances, and there are just a few cases where hazard was assessed specifically for this route of exposure.

To alleviate this uncertainty, the intradermal route was considered in RAC's assessment whenever possible (i.e. for skin irritants or corrosives, or eye damage or irritant chemicals), and in the case where data from oral exposure were used for risk assessment, a correction factor for oral absorption was considered and used where relevant (e.g., for copper and barium).

In addition, RAC notes that the exposure scenario proposed by the Dossier Submitter takes into account realistic worst case (e.g., amount of tattoo ink injected in one tattooing session) or even worst case (e.g., assumption of complete bioavailability of injected tattoo inks in a person obtaining a full-coloured full-body tattoo). Therefore, despite uncertainties due to limited data available on hazards, exposure and risks related to chemicals used in tattoo inks, this scenario could be expected to overestimate the risks.

Another important uncertainty relates to unknown decomposition products of tattoo colourants in the skin, either due to skin metabolism or due to sun exposure or tattoo removal techniques (e.g., by laser). Presently, available data are insufficient to adequately address these issues.

Practical concentration limit of 0.1% for azo colourants is proposed in order to avoid intentional use of these colourants as main components. There is an uncertainty, however, whether azo colourants could be present as impurities, and therefore, present in tattoo inks in concentrations below 0.1% w/w.

Uncertainties in epidemiological data impede reliable estimation of incidence and prevalence of adverse health effects related to substances present in tattoo inks.

Unknown health risks of pigments injected in a form of nanoparticles pose another uncertainty, discussed in section B.1.2.4 as well as decomposition of tattoo inks during laser treatment.

Nevertheless, RAC is of the opinion that these uncertainties do not present the obstacles for implementation of the proposed restriction. On the contrary, RAC considers that this restriction could be an important initiative for the scientific community to fill the above stated knowledge gaps. New relevant data, incorporated into any updates of this restriction, are expected to alleviate the uncertainties and increase the restriction effectiveness, as discussed in section B.3.2.3.

SEAC

B.4.4. Summary of proposal:

The proposed restriction options (RO1 and RO2) remain proportionate even when

allowance for uncertainties is made, i.e., the volume of tattoo inks and PMU on the market, the share of alternatives currently on the market, the anticipated price increase and their combined impact. The combination of low volume/low share of alternatives/high price difference leads to the highest deterioration of the cost-effectiveness of RO1 by 65%. For the proposed restriction options to break even in the worst case scenario, 2 050 surgical removals due to complication of tattoo inks would need to be avoided (calculated using cost of illness (COI) plus low WTP values) or 620 (COI plus high WTP values). This is respectively about 0.12% or 0.04% of the estimated number of people getting tattoos for the first time each year in EEA22.

It is reasonable to expect that these cases would be avoided as a result of the proposed restriction options as the estimated average prevalence rate of tattoo complications is 1.7% and not all costs are taken into account.

In addition, removal of tattoos due to an allergic or papulo-nodular reaction is just one group of the health outcomes. As stated in section Human Health Impact, a number of people experience complications that require topical or systemic corticosteroids as well as experience mild ongoing complaints from their tattoos and PMU. This is in addition to the potential contribution of tattoo ink and PMU exposure to carcinogenic, reproductive, developmental and other systemic adverse effects.

B.4.5. SEAC conclusion(s):

Uncertainties regarding the cost assessment and their possible implications on the proportionality assessment have been discussed in section B.3.6.5, and it is reminded here that those related to administrative and testing costs could be significant.

SEAC also notes that given the lack of technical information on tattoo inks composition and pigments manufacturing technical constraints, it is not possible to assess the difference between the three restriction options in terms of costs and benefits.

B.4.6. Key elements underpinning the SEAC conclusion(s):

Please see relevant sections on costs, benefits and proportionality for justification.

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Appendix 1: Supplementary Tables A to RAC and SEAC modified Restriction Option 1

This Annex includes supplementary tables to the proposed restriction.

Table A contains the specified concentration limits for methanol, PAHs, other impurities listed in Table 3 of CoE ResAP(2008)1, PAAs, and azo dyes, proposed by RAC.

Table 13. Supplementary Table A to RAC and SEAC modified RO1

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
Mercury		231-106-7	7439-97-6	0.00005% w/w
Nickel		231-111-4	7440-02-0	0.0005% w/w
Organometallic tin		231-141-8	7440-31-5	0.00005% w/w
Antimony		231-146-5	7440-36-0	0.00005% w/w
Arsenic		231-148-6	7440-38-2	0.00005% w/w
Barium**		231-149-1	7440-39-3	0.05% w/w
Cadmium		231-152-8	7440-43-9	0.00005% w/w
Chromium‡		231-157-5	7440-47-3	0.00005% w/w
Cobalt		231-158-0	7440-48-4	0.00005% w/w
Copper**		231-159-6	7440-50-8	0.025% w/w
Zinc**		231-175-3	7440-66-6	0.2% w/w
Lead		231-100-4	7439-92-1	0.00007% w/w
Selenium		231-957-4	7782-49-2	0.0002% w/w
Benzo[a]pyrene	BaP, Benzo[def]chrysene	200-028-5	50-32-8, 63466-71-7	0.0000005% w/w
Polycyclic-aromatic Hydrocarbons (PAH), classified as carcinogenic or mutagenic categories 1A, 1B and 2				0.00005% w/w (individual concentrations)
Methanol		200-659-6	67-56-1	11% w/w
o-Anisidine**	2-methoxyaniline	201-963-1	90-04-0	0.0005% w/w
o-toluidine**	2-aminotoluene	202-429-0	95-53-4	0.0005% w/w
3,3'-dichlorobenzidine**	4-(4-amino-3-chlorophenyl)-2-chloroaniline	202-109-0	91-94-1	0.0005% w/w
4-methyl-m-phenylendiamine**	2,4-toluenediamine	202-453-1	95-80-7	0.0005% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
4-chloroaniline**	-	203-401-0	106-47-8	0.0005% w/w
5-nitro-o-toluidine**	-	202-765-8	99-55-8	0.0005% w/w
3,3'-dimethoxybenzidine**	o-dianisidine	204-355-4	119-90-4	0.0005% w/w
4,4'-bi-o-toluidine**	-	204-358-0	119-93-7	0.0005% w/w
4,4'-Thiodianiline**	-	205-370-9	139-65-1	0.0005% w/w
4-chloro-o-toluidine**	-	202-441-6	95-69-2	0.0005% w/w
2-naphthylamine**	-	202-080-4	91-59-8	0.0005% w/w
Aniline**	aniline	200-539-3	62-53-3	0.0005% w/w
Benzidine**	1,1'-biphenyl-4,4'-diamine 4,4'-diaminobiphenyl biphenyl-4,4'-ylenediamine	202-199-1	92-87-5	0.0005% w/w
p-toluidine**	4-aminotoluene	203-403-1	106-49-0	0.0005% w/w
2-methyl-p-phenylenediamine**	2,5-toluenediamine	202-442-1	95-70-5	0.0005% w/w
Biphenyl-4-ylamine**	4-Aminobiphenyl xenylamine 4-aminobiphenyl xenylamine	202-177-1	92-67-1	0.0005% w/w
4-o-tolylazo-o-toluidine**	Solvent Yellow 3/ CI 11160 4-amino-2',3-dimethylazobenzene AAT fast garnet GBC base o-aminoazotoluene	202-591-2	97-56-3	0.0005% w/w
4-methoxy-m-phenylenediamne**	2,4-diaminoanisole	210-406-1	615-05-4	0.0005% w/w
4,4'-methylenedianiline**	4,4'-diaminodiphenylmethane (MDA)	202-974-4	101-77-9	0.0005% w/w
4,4'-methylenedi-o-toluidine**	-	212-658-8	838-88-0	0.0005% w/w
6-methoxy-m-toluidine**	p-cresidine	204-419-1	120-71-8	0.0005% w/w
4,4'-methylenebis[2-chloroaniline]**	2,2'-dichloro-4,4'-methylenedianiline (MOCA)	202-918-9	101-14-4	0.0005% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
4,4'-oxydianiline**	p-aminophenyl ether	202-977-0	101-80-4	0.0005% w/w
2,4,5-trimethylaniline**	-	205-282-0	137-17-7	0.0005% w/w
4-Aminoazobenzene**	4-phenylazoaniline Solvent Yellow 1/ CI 11000	200-453-6	60-09-3	0.0005% w/w
p-Phenylenediamine**		203-404-7	106-50-3	0.0005% w/w
Sulphanilic acid**	4-aminobenzenesulphonic acid	204-482-5	121-57-3	0.0005% w/w
4-amino-3-fluorophenol**	-	402-230-0	399-95-1	0.0005% w/w
2,6-xylidine	2,6-dimethylaniline	201-758-7	87-62-7	0.0005% w/w
6-amino-2-ethoxynaphthaline			293733-21-8	0.0005% w/w
2,4-xylidine		202-440-0	95-68-1	0.0005% w/w
Pigment Red 7 (PR7)/CI 12420	N-(4-chloro-2-methylphenyl)-4-[(4-chloro-2-methylphenyl)azo]-3-hydroxynaphthalene-2-carboxamide	229-315-3	6471-51-8	0.1% w/w
Pigment Red 9(PR9)/CI 12460	4-[(2,5-dichlorophenyl)azo]-3-hydroxy-N-(2-methoxyphenyl)naphthalene-2-carboxamide	229-104-6	6410-38-4	0.1% w/w
Pigment Red 15 (PR15)/CI 12465	4-[(4-chloro-2-nitrophenyl)azo]-3-hydroxy-N-(2-methoxyphenyl)naphthalene-2-carboxamide	229-105-1	6410-39-5	0.1% w/w
Pigment Red 210(PR210)/CI 12477		612-766-9	61932-63-6	0.1% w/w
Pigment Orange 74 (PO74)			85776-14-3	0.1% w/w
Pigment Yellow 65 (PY65)/CI 11740	2-[(4-methoxy-2-nitrophenyl)azo]-N-(2-methoxyphenyl)-3-oxobutyramide	229-419-9	6528-34-3	0.1% w/w
Pigment Yellow 74 (PY74)/CI 11741	2-[(2-methoxy-4-nitrophenyl)azo]-N-(2-methoxyphenyl)-3-oxobutyramide	228-768-4	6358-31-2	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
Pigment Red 12 (PR12)/CI 12385	3-hydroxy-4-[(2-methyl-4-nitrophenyl)azo]-N-(o-tolyl)naphthalene-2-carboxamide	229-102-5	6410-32-8	0.1% w/w
Pigment Red 14 (PR14)/CI 12380	4-[(4-chloro-2-nitrophenyl)azo]-3-hydroxy-N-(2-methylphenyl)naphthalene-2-carboxamide	229-314-8	6471-50-7	0.1% w/w
Pigment Red 17 (PR17)/CI 12390	3-hydroxy-4-[(2-methyl-5-nitrophenyl)azo]-N-(o-tolyl)naphthalene-2-carboxamide	229-681-4	6655-84-1	0.1% w/w
Pigment Red 112 (PR112)/CI 12370	3-hydroxy-N-(o-tolyl)-4-[(2,4,5-trichlorophenyl)azo]naphthalene-2-carboxamide	229-440-3	6535-46-2	0.1% w/w
Pigment Yellow 14 (PY14)/CI 21095	2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(2-methylphenyl)-3-oxobutyramide]	226-789-3	5468-75-7	0.1% w/w
Pigment Yellow 55 (PY55)/CI 21096	2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(2-methylphenyl)-3-oxobutyramide]	226-789-3	6358-37-8	0.1% w/w
Pigment Red 2 (PR2)/ CI 12310	4-[(2,5-dichlorophenyl)azo]-3-hydroxy-N-phenylnaphthalene-2-carboxamide	227-930-1	6041-94-7	0.1% w/w
Pigment Red 22 (PR22)/ CI 12315	3-hydroxy-4-[(2-methyl-5-nitrophenyl)azo]-N-phenylnaphthalene-2-carboxamide	229-245-3	6448-95-9	0.1% w/w
Pigment Red 146 (PR146)/ CI 12485	N-(4-chloro-2,5-dimethoxyphenyl)-3-hydroxy-4-[[2-methoxy-5-[(phenylamino)carbonyl]phenyl]azo]naphthalene-2-carboxamide	226-103-2	5280-68-2	0.1% w/w
Pigment Red 269 (PR269)/ CI 12466	N-(5-chloro-2-methoxyphenyl)-3-hydroxy-4-[[2-methoxy-5-[(phenylamino)carbonyl]phenyl]azo]naphthalene-2-carboxamide	268-028-8	67990-05-0	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
Pigment Orange16 (PO16)/ CI 21160	2,2'-[(3,3'-dimethoxy[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[3-oxo-N-phenylbutyramide]	229-388-1	6505-28-8	0.1% w/w
Pigment Yellow 1 (PY1)/ CI 11680	2-[(4-methyl-2-nitrophenyl)azo]-3-oxo-N-phenylbutyramide	219-730-8	2512-29-0	0.1% w/w
Pigment Yellow 12 (PY12)/CI 21090	2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[3-oxo-N-phenylbutyramide]	228-787-8	6358-85-6	0.1% w/w
Pigment Yellow 87 (PY87)/ CI 21107:1	2,2'-[(3,3'-dichloro-4,4'-biphenylylene)bis(azo)]bis[2',5'-dimethoxyacetoacetanilide]	239-160-3	15110-84-6, 14110-84-6	0.1% w/w
Pigment Yellow 97 (PY97)/ CI 11767	N-(4-chloro-2,5-dimethoxyphenyl)-2-[[2,5-dimethoxy-4-[(phenylamino)sulphonyl]phenyl]azo]-3-oxobutyramide	235-427-3	12225-18-2	0.1% w/w
Pigment Orange 13 (PO13)/ CI 21110	4,4'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one]	222-530-3	3520-72-7	0.1% w/w
Pigment Orange 34 (PO34)/ CI 21115	4,4'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[2,4-dihydro-5-methyl-2-(p-tolyl)-3H-pyrazol-3-one]	239-898-6	15793-73-4	0.1% w/w
Pigment Yellow 83 (PY83)/ CI 21108	2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(4-chloro-2,5-dimethoxyphenyl)-3-oxobutyramide]	226-939-8	5567-15-7	0.1% w/w
Solvent Red 1 (SR1)/ CI 12150	1-[(2-methoxyphenyl)azo]-2-naphthol	214-968-9	1229-55-6	0.1% w/w
Acid Orange 24 (AO24)/ CI 20170	Sodium 4-[[3-[(dimethylphenyl)azo]-2,4-dihydroxyphenyl]azo]benzenesulphonate	215-296-9	1320-07-6	0.1% w/w
Solvent Red 23 (SR23)/ CI 26100	1-(4-(phenylazo)phenylazo)-2-naphthol	201-638-4	85-86-9	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
Acid Red 73 (AR73)/ CI 27290	Sodium 6-hydroxy-5-(4-phenylazophenylazo)naphthalene-2,4-disulphonate	226-502-1	5413-75-2	0.1% w/w
Disperse Yellow 3/ CI 11855	N-[4-[(2-hydroxy-5-methylphenyl)azo]phenyl]acetamide	220-600-8	2832-40-8	0.1% w/w
Acid Green 16	sodium 4-{[4-(diethylamino)phenyl][4-(diethyliminio)cyclohexa-2,5-dien-1-ylidene]methyl}naphthalene-2,7-disulfonate	603-214-8	12768-78-4	0.1% w/w
Acid Red 26	Disodium 1-(2,4-dimethylphenylazo)-2-hydroxynaphthalene-3,6-disulphonate	223-178-3	3761-53-3	0.1% w/w
Acid Violet 17	Hydrogen [4-[[4-(diethylamino)phenyl][4-[ethyl(3-sulphonatobenzyl)amino]phenyl]methylene]cyclohexa-2,5-dien-1-ylidene](ethyl)(3-sulphonatobenzyl)ammonium, sodium salt	223-942-6	4129-84-4	0.1% w/w
Basic Red 1 , Basic red 1	9-[2-(ethoxycarbonyl)phenyl]-3,6-bis(ethylamino)-2,7-dimethylxanthylium chloride	213-584-9	989-38-8	0.1% w/w
Disperse Blue 106	Ethanol, 2-[ethyl[3-methyl-4-[2-(5-nitro-2-thiazolyl)diazenyl]phenyl]amino]-	602-285-2	12223-01-7	0.1% w/w
Disperse Blue 124	Disperse Blue 124	612-788-9	61951-51-7	0.1% w/w
Disperse Blue 35	C.I. dDisperse Blue 35	602-260-6	12222-75-2	0.1% w/w
Disperse Orange 37	Propanenitrile, 3-[[4-[2-(2,6-dichloro-4-nitrophenyl)diazenyl]phenyl]ethylamino]-	602-312-8	12223-33-5	0.1% w/w
Disperse Red 1	2-[ethyl[4-[(4-nitrophenyl)azo]phenyl]amino]ethanol	220-704-3	2872-52-8	0.1% w/w
Disperse Red 17	2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol	221-665-5	3179-89-3	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
Disperse Yellow 9	N-(2,4-dinitrophenyl)benzene-1,4-diamine	228-919-4	6373-73-5	0.1% w/w
Pigment Violet 3	4-[(4-Aminophenyl)-(4-methyliminocyclohexa-2,5-dien-1-ylidene)methyl]aniline	603-635-7	1325-82-2	0.1% w/w
Pigment Violet 39	Methanaminium, N-[4-[bis[4-(dimethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene]-N-methyl-, molybdatephosphate	264-654-0	64070-98-0	0.1% w/w
Solvent Yellow 2	4-dimethylaminoazobenzene	200-455-7	60-11-7	0.1% w/w

**Soluble. ‡Chromium VI.

Appendix 2: Details of hazard assessments of substance groups and individual substances.

1. Substances with predominantly non-threshold health hazards evaluated qualitatively

Carcinogenicity and mutagenicity

The Dossier Submitter assumes that it is probable that tattoo inks may contain, primarily as impurities, substances having harmonised classification as carcinogenic or mutagenic substances category 1 and 2 other than those listed in Table A. So far, information on their possible use in tattoo inks is available for less than 5% of these substances. This is possibly because the presence of many of them has not been specifically investigated. In order to control a risk that such substances may create (in current and future use in tattoo inks), they are included in the scope of this restriction by the Dossier Submitter in RO1 and RO2. RAC has modified RO1 primarily to introduce changes to concentration limits.

The majority of carcinogens and all mutagens are considered as non-threshold substances, thus, it is not possible to determine a very low dose at which a substance will not cause a carcinogenic or a mutagenic effect.

Some carcinogenic substances act as initiators (DNA-reactive mutagens), while others promote proliferation of mutated cells without reacting with DNA (i.e. they are non-genotoxic carcinogens), or contribute to progression from benign to malignant cells/tumours. Many mutagens are also carcinogens, and act both as an initiator and a promotor.

The carcinogenic and mutagenic substances in the scope of this restriction also include some azo colourants[75], PAAs, and polycyclic aromatic hydrocarbons (PAH) that have such classifications.

Taking into account the mechanism of action, it is justified to include in the scope of the restriction all substances classified as carcinogenic (C) or mutagenic (M) Category 1A, 1B or 2. That is substances having a harmonised classification in Annex VI of Regulation 1272/2008 (CLP)) except those classified only with hazard statements H350i (May cause cancer by inhalation), H351i (Suspected of causing cancer by inhalation), H340i (May cause genetic defects via inhalation) and H341i (Suspected of causing genetic defects by inhalation). The exemption of the substances classified as carcinogens or mutagens only by the inhalation route is justified by a fact that in order to assign such classifications, it has to be proven that they do not act by other routes of exposure, that is, dermal and oral. In practice, this requires availability of considerable toxicological evidence and only for very few substances it is possible to demonstrate that they are carcinogenic or mutagenic only by inhalation route.

It is proposed to include category 1A and 1B CM substances, as well as CM category 2 substances in one group as the majority of the CM substances are assumed to be non-

[75] The Dossier Submitter has assumed that the azo colourants decompose and some of the decomposition products are carcinogenic or mutagenic.

threshold substances. This is even if it is suspected that some of them work via a threshold, as may be the case for aneugens (Elhajouji et al., 2011) or C promotors (Neumann, 2009). For CM category 2 substances, there is a concern that they are only suspected human carcinogens and may induce heritable mutations in the germ cells of humans, based on limited evidence of carcinogenicity and mutagenicity. In CLP, substances may be assigned to Carc. category 2 if evidence of carcinogenicity is restricted to a single experiment, or is only seen as benign neoplasms, or only as promoting activity in a narrow range of tissues or organs.

RAC agrees with the Dossier Submitter that for a substance possessing carcinogenic properties the establishment of a dose-response relationship to characterise its potency requires a considerable amount of human or animal data, which is not possible to gather for the majority of them. In addition, there are no data on carcinogenic potency of substances with harmonised classifications specifically following the intradermal route of exposure. Therefore, it is reasonable to apply a qualitative approach for the characterisation of dose/concentration-response for human health.

For all CM categories, substances are not assigned to a particular hazard category based on whether or not they work via a threshold. Therefore, even if a threshold exists for some of the carcinogenic substances in tattoo inks, the recommended RMM/OCs would still be to avoid contact with them (CSA Guidance R.8) (ECHA, 2012) and this would only be possible in tattoo inks by preventing the substances being in the inks. This principle is reflected in the RO1 in which any presence of carcinogenic or mutagenic substances, category 1A, 1B and 2 (excluding those substances classified only with the hazard statements H350i) is not allowed, which in practice means that concentrations of such substances in tattoo inks should be below the detection limit of available analytical methods. However, this, as was pointed out in advice of the Forum for Exchange of Information on Enforcement (Forum), leads to difficulties ensuring similar enforcement of this restrictions in different countries and may highly depend upon the skills, equipment and quality of work of chemical laboratories asked to make measurements of carcinogenic substances in tattoo inks. This was the basis of the Dossier Submitters proposing a practical concentration limit[76] RO2, namely: tattoo inks shall not be placed on the market if they contain these substances in concentrations greater than the relevant generic concentration limit (GCL) or specific concentration limit (SCL) set in Regulation (EC) No 1272/2008.

Indeed, according to Regulation (EC) No 1272/2008 (CLP), the tattoo ink shall be classified

[76] A practical concentration limit is a maximum concentration of hazardous chemical substance in the mixture, which aims at reduction of the health risk posed by the substance due to allowed uses of that mixture. The limit takes into account a concentration limit based on risk but also takes into account other issues such as uncertainties, detection or identification limits, etc. It can also take into account the concentration required to prevent intentional use of a substance. The practical limit might be needed due to limited data meaning it is not possible to determine the exact dose-response relationship between levels of exposure and magnitude of risk for that substance. It may be set for one substance or for a group of substances posing the same health hazards such as e.g. carcinogenicity, mutagenicity, skin sensitisation or eye/skin damage. The practical concentration limit serves as a reference value with which the measured concentrations value in the mixture is compared, thus it is a tool in risk management for those dealing with mixture containing this substance.

as a carcinogen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 carcinogen and is present at or above the appropriate generic concentration limit (GCL). These limits are ≥ 0.1 % for carcinogens Category 1A and 1B, and ≥ 1.0 % for carcinogens category 2. However, some specific substances have lower specific concentration limits, which would also justify the classification of tattoo ink as mixture. These limits could be as low as 0.001%.

The generic and specific concentration limits set in Regulation (EC) No 1272/2008 reflect to some extent the carcinogenic potency of the substance having harmonised classification. However, these limits are intended to be used for communication on health hazard of the mixtures, and not for risk assessment, since they were not based on risk assessment for individual substances. Therefore, in the opinion of RAC they should not be used as admissible concentration limits for carcinogenic and mutagenic substances in tattoo inks as proposed by Dossier Submitter in RO2.

Skin sensitisation

The Dossier Submitter proposed that all substances with harmonised classification as skin sensitiser Category 1, 1A or 1B are restricted in tattoo inks (415 substances classified only as skin sensitisers, and 1 159 classified as skin sensitisers with other relevant classifications), based on their intrinsic hazardous properties to induce reaction of allergic sensitisation, leading to allergic contact dermatitis. Sensitisation reaction occurs when these substances are applied to the epidermis or injected into the dermis. It has been reported that lower doses are needed to induce sensitisation reaction with intradermal compared to topical application since intradermal application bypasses the limitation of skin penetration (present with topical mode of exposure) (e.g., Frankild et al. 2000), but data that would enable quantification of this difference are not available at the present moment.

Twenty-two skin sensitising substances have been identified in tattoo inks (according to the Joint Research Centre; JRC 2015b). However, since both present and future use of other substances with the same hazardous property cannot be excluded, RAC supports the Dossier Submitter's proposal to include all substances with harmonised classification for skin sensitisation in the scope.

For this endpoint a qualitative approach was chosen by the Dossier Submitter. Although skin sensitisers theoretically might have thresholds, data is very rarely available to build a dose-response or set a reliable threshold. For illustration, ECHA Guidance states that "deriving the safe use levels for skin sensitisation can be problematic and may be associated with considerable uncertainty" (ECHA Guidance R.7a). It should be stressed, as well, that available animal and human data are not in this case very suitable to build a reliable dose-response curve, since they are predominantly derived from topical application route (e.g., LLNA and Buehler test in animals, patch test in humans), while stronger response could be expected for intradermal route, applied in tattooing. For all these reasons, RAC agrees with the Dossier Submitter that a DNEL could not be set for this hazard endpoint.

Skin and eye irritant/corrosion

RAC agrees with the Dossier Submitter's proposal that all substances with harmonised classification as skin corrosives or irritants, or as substances causing serious eye damage or

eye irritant should be restricted in tattoo inks. This is based on the assumption that these substances can induce at least the same, if not more severe effects when they are introduced into the skin or eyes than when they are applied topically.

A significant amount of tattooed people report skin problems after tattooing (e.g. about 68% in a study performed by Kluegl, et al., 2010). There are difficulties in distinguishing allergic and non-allergic skin reactions (due to the reasons stated in the Background Document, Annex B.5.3/4), and it is hard to differentiate, especially for early symptoms, reactions due to skin damage from the tattoo procedure itself from reactions caused by the chemicals in a tattoo ink.

RAC considers, nevertheless, that it is unlikely that all local skin reactions are allergic or due to tattooing procedure only, and agrees with the Dossier Submitter that a part of the reactions can be irritative in nature[77]. Therefore, RAC considers that available human and animal data, as well as intrinsic property of these substances to induce irritation or corrosion, indicate risk which justifies their restriction in tattoo inks.

This is supported by the following considerations:

- Although it is not known to what degree non-allergic, inflammatory, non-infectious reactions are due to irritant effect of the injected chemicals, and not due to mechanical damage of tissues related to tattooing procedure, the risk of aggravating mechanical injury by chemically induced cell damage cannot be either excluded or quantified.
- It has been recognised that the presence of irritants, even at doses inducing slight irritation (e.g. 0.25% or 1% sodium lauryl sulphate applied topically), can significantly enhance allergogenic effects of simultaneously applied chemicals, both in induction and elicitation phase (McFadden and Basketter, 2000; Nagtegaal et al., 2012; Schwitulla et al., 2014). This effect is considered to be caused not only by increased permeability of epidermal barrier (which is not relevant for tattooing procedure), but also by an induction of inflammatory cytokine response, relevant for intradermal exposure route as well (McFadden et al., 2000; Schwitulla et al., 2014). This issue is especially relevant for skin sensitising chemicals without harmonised classification that are not yet regulated by other means (e.g. by CPR or BPR), and could be, therefore, still present in tattoo inks.
- Data comparing irritative potency of topically and intradermally applied drugs in human subjects (Brockow et al. 2013) and known irritants in animals (Sekizawa et al., 1994), supports the Dossier Submitter's assumption that skin or eye irritants can induce at least the same, if not more severe effects when they are injected into the skin or eyes than when applied topically.

Among approximately 1 500 substances with harmonised classification for these hazard classes, 29 have been found in tattoo inks, out of which 11 are also skin sensitisers and 3 are also classified as carcinogenic/mutagenic. Skin/eye irritants/corrosives are expected to

[77] According to clinical criteria set by Serup, et al. (2015b), 13% of 493 tattoo reactions (reported by patients at the "Tattoo Clinic" at the Department of Dermatology at Bispebjerg University Hospital, Copenhagen) were classified as non-allergic, inflammatory, non-infectious reactions.

be present in tattoo inks mainly as preservatives, dispersing agents or impurities.

Qualitative risk assessment is proposed by the Dossier Submitter for this endpoint as well, since available *in vitro* and *in vivo* studies usually provide only qualitative (yes or no) output, or semi-quantitative information on potency (e.g. corrosive after certain duration of exposure, or higher or lower scores for erythema, oedema and other irritative effects). Therefore, setting reliable DN(M)ELs was not possible for these substances.

2. **Substances with non-threshold health hazards evaluated qualitatively and concentration limits set quantitatively (DMELs)**

The risk from this group of substances was qualitatively assessed by the Dossier Submitter as for group 1 above. In these cases a reliable dose descriptor could not be set as the substances are either carcinogens or mutagens (PAAs), are assumed to decompose to CM substances (azo colourants), or have non-threshold neurodevelopmental effects (lead).

RAC also agrees with the Dossier Submitter that it is not possible to introduce a complete ban of all hazardous substances in tattoo inks. Therefore, in some cases there was a need for setting a concentration limit for hazardous substances and impurities in tattoo inks to protect the consumers from adverse health effects. The concentration limits in the Dossier Submitters proposal were based on the DMELs for these substances. To derive the DMEL values for non-threshold carcinogenic substances, the maximum level of indicative tolerable lifetime excess cancer risk for consumers was assumed to be 10^{-6}, in accordance with ECHA guidance R.8.1.1 (ECHA, 2012).

Assessment factors were applied in accordance with ECHA Guidance R.8 (ECHA, 2012). In most of the assessments an assessment factor of 10 was applied for intra-species variation and another assessment factor of 10 was applied for inter-species variation. Modification of the dose descriptors and the application of additional assessment factors are given in the respective chapters for the relevant endpoints/substances (such as assessment factors for differences in exposure duration, issues related to dose-response, quality of whole database).

Azo colourants and primary aromatic amines (PAAs)

Azo colourants are important colourants in tattooing, comprising more than 50% of the colourants used (mainly in red, yellow and orange tattoo inks) (JRC 2015b), and therefore, they have been specifically addressed by the Dossier Submitter.

Primary aromatic amines (PAAs) might be present in tattoo inks as impurities (e.g. as non-reacted remnants in the final azo colourant), as products of ultraviolet decomposition (sunlight or laser light), or enzymatic or bacterial decomposition of azo colourants, or could be added to an azo colourant for achieving a specific nuance of a colour.

Hazard assessment of PAAs

RAC agrees with the Dossier Submitter to choose carcinogenicity and skin sensitisation as the most sensitive endpoints for hazard assessment of PAAs, and carcinogenicity for risk assessment and setting of concentration limit (since the available data were not sufficient for an evaluation of potency or threshold value for skin sensitisation). PAAs are well known for their carcinogenicity, and many of them are skin sensitisers (Table A in the Background

Document, POISINDEX 2018, Bafana et al., 2011). Risk assessment based on carcinogenicity is expected to protect exposed tattooed subject also from other toxic effects of PAAs, such as anaemia, methaemoglobinaemia, or kidney and liver damage (POISINDEX 2018, Bafana et al., 2011), and lower the risk of allergic sensitisation.

All PAAs classified for health hazards considered relevant for tattooing (i.e. carcinogenicity, mutagenicity, reproductive toxicity, skin sensitisation, corrosion or significant irritation of skin or eye), as well as those covered by the CPR (Annex II and Annex IV) or CoE ResAP(2008)1 (Table 1), are in the scope of this restriction proposal. However, analysis of tattoo inks on the EU market showed that it is not feasible to expect (at least at the present moment) to achieve a concentration of carcinogenic, mutagenic or skin sensitising PAAs below the limit of detection in many tattoo inks (as set in RO1), without losing important diversity of colours. On the other hand, as a result of the risk assessment, the Dossier Submitter concluded that generic classification limits for carcinogenicity (as set in RO2) are not protective enough.

The Dossier Submitter, therefore, proposed to set risk-based concentration limit for **29 PAAs** which:

- possess carcinogenic, mutagenic or skin sensitising properties, and
    - have been identified among the 67 azo colourants with information that they can be found in tattoo inks (JRC, 2015b), or
    - are listed in Table 1 of CoE ResAP(2008)1[78]; or
    - theoretically may occur in tattoo inks as decomposition products (by amide hydrolysis only or by both amide hydrolysis and reductive cleavage) of azo colourants used in tattoo inks (among 67 azo colourants identified in tattoo inks), or
    - theoretically may occur in tattoo inks as non-reacted impurities from the production process or as decomposition products (reductive cleavage of azo bond) of azo colourants from Table 1 in CoE ResAP (2008)1;
- or are restricted in REACH (Annex XVII, entry 43 - related to restriction of azodyes which may release carcinogenic PAAs listed in Appendix 8, in textiles and leather articles which may come into direct and prolonged contact with the human skin or oral cavity).

These PAAs are listed in Table A in the Background Document.

RAC agrees with the Dossier Submitter's proposal, including the proposal to set specific concentration limit also for PAAs restricted in REACH which have not yet been found in tattoo inks, and are not expected to be found due to the structure of known azo colourants currently used. This approach aims to prevent substitution to other azo colourants that may also decompose to these PAAs.

RAC does not agree with the Dossier Submitter to exclude the two PAAs from Table 1 of CoE

[78] CoE ResAP(2008)1 Table 1 – List of aromatic amines, particularly with regard to their carcinogenic, mutagenic, reprotoxic and sensitising properties, which should neither be present in tattoos and PMU products nor released from azo-colorants

ResAP(2008)1 (6-amino-2-ethoxynaphthaline CAS 293733-21-8 and 2,4-xylidine EC 202-440-0 / CAS 95-68-1). The two PAAs do not have harmonised classification and relevant background documents for the inclusion of these PAAs in the resolution are not available. Therefore, RAC proposes that these two PAAs are included in the scope until adequate data for risk assessment are available, which is in line with general approach taken in this restriction proposal to include in the scope substances recommended to be restricted in tattoo inks by the CoE resolutions.

DMEL derivation for PAAs: Hazard assessment has been performed for the ten PAAs found in significant amounts in a Danish survey of tattoo inks (DEPA, 2012) (i.e., aniline, o-anisidine, 4-chloroaniline, 4- chloro-o-toluidine, 3,3'-dichlorobenzidine, 4-methyl-m-phenylenediamine, 4-methoxy-m-phenylenediamine, 2-naphthylamine, 5-nitro-o-toluidine and o-toluidine). Since carcinogenic effect was considered as the critical effect in relation to tattooing for the selected PAAs, and it is considered that there is no threshold for the carcinogenic effects, DMELs were derived to set appropriate concentration limit in tattoo inks. Out of the ten selected PAAs, it was possible to establish DMEL values only for aniline and o-anisidine, since for other eight PAAs the data was considered insufficient and/or inadequate.

For **aniline** (harmonised classification as Carc. 2, Muta. 2, Acute Tox. 3 via oral, dermal and inhalation route, STOT RE 1, Eye Dam. 1, Skin Sens. 1), the DMEL is based on the relevant EU risk assessment report (RAR). The lowest concentration causing an effect was for carcinogenicity (primarily in the spleen), with a rat T25 of 46 mg/kg bw per day. Applying an assessment factor of 10 for extrapolation from rats to humans, HT25 (T25 for humans) of 4.6 mg/kg bw per day for oral exposure was calculated, and applying a high to low dose risk extrapolation factor (HtLF) of 250 000[79] to this value, a DMEL of approximately 2 x 10^{-5} mg/kg bw per day was derived.

For **o-anisidine** (harmonised classification as Carc. 1B, Muta. 2, Acute Tox. 3 via oral, dermal and inhalation route), the DMEL is based also on the EU RAR. Although carcinogenicity was considered as the critical effect (mainly tumours in the bladder), uncertainty remained as to whether o-anisidine possesses skin sensitising potential. Based on rat T25 of 39.7 mg/kg bw/day, HT25 of 9.9 mg/kg bw/day was derived by applying an assessment factor of 4 for inter-species extrapolation[80]. Applying HtLF of 250 000 to HT25, a DMEL of approximately 4 x 10^{-5} mg/kg bw/day was derived[81].

The Dossier Submitter considered that all PAAs with harmonised classification as carcinogenic are very similar, and, therefore, applied grouping approach, with the lower DMEL of 2 x 10^{-5} mg/kg bw per day, carried forward in the risk assessment for PAAs.

[79] The 'default' for the 10^{-6} lifetime risk when T25 is used as a PoD (according to ECHA Guidance chapter 8 appendix R.8-6 and 8-7)

[80] According to the EU-RAR, the assessment factor of 4 was taken into account for metabolic rate scaling (rat-to-human), but no further details are available in the EU-RAR.

[81] Beside the DMEL, a DNEL could be also derived. Based on the data from 28-day study in rats, DNEL of 0.03 mg/kg bw/day was calculated by the Dossier Submitter, and in the EU RAR, 'human NAEL' of 0.07 mg/kg bw/day was derived. However, these values are higher than DMEL, and carcinogenicity was considered as the most sensitive outcome.

There are several uncertainties in the described approach:

- the assessment has been limited only to selected PAAs, and it is uncertain whether it is representative for the whole group;
- the EU RAR approach has been adopted by the Dossier Submitter, although some details of the assessment (e.g. regarding assessment factors) were not available;
- there is a possibility that not yet identified carcinogenic, mutagenic or skin sensitising PAAs are present (or will be present) in tattoo inks.

These uncertainties, however, should be seen in the following context:

- aniline and o-anisidine are among the three most frequently observed PAAs in tattoo inks (third one is o-toluidine) (DEPA, 2012);
- the DMELs for aniline and o-anisidine are in the same order of magnitude;
- although the key study for carcinogenicity of 3,3'-dichlorobenzidine has significant limitations and is not considered reliable enough for setting DMEL for this restriction proposal, the guidance value based on this study (which corresponds to a DMEL) is calculated to be in the range of 1.48×10^{-4} - 1.48×10^{-5} mg/kg bw, which is rather similar to the DMEL proposed for selected PAAs (2×10^{-5} mg/kg bw per day);
- even if not yet identified PAAs of concern are (or will be) present in tattoo inks, they will still be restricted (if classified as carcinogenic, mutagenic, or skin sensitising), although probably at different concentration limit (according to the CLs set for carcinogenic/mutagenic substances or skin sensitising substances) than that proposed for selected 29 PAAs.

In addition, the calculated DMEL is very similar if correction factor for oral availability of aniline (80% in rats; Kao et al., 1978) is applied to rat's T25: 0.000015, instead of 0.000018 derived without correction factor (aniline data were used for correction factor since toxicokinetics data for o-anisidine are very limited).

RAC agrees, in general, with the Dossier Submitter's approach in deriving a DMEL for PAAs. Nevertheless, RAC notes that whereas SCOEL assumes a lack of threshold for o-anisidine, a TWA is set for aniline based on a MoA-based threshold (methaemoglobinaemia). On the other hand, no threshold value has been used for o-anisidine.

Another issue is a different assessment factor for aniline and o-anisidine (10 and 4, respectively) applied for rat to human extrapolation in the EU RAR. RAC notes that, according to ECHA Guidance[82], while for threshold substances, the default interspecies assessment factor is 10 (4 for allometric scaling in case of rat study as PoD multiplied by 2.5 for remaining interspecies differences), for non-threshold substances the interspecies assessment factor only consists of the allometric scaling factor. Namely, in contrast to threshold substances, the default factor of 2.5 for remaining interspecies differences is not to be applied, because the

[82] ECHA Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, 2012

high-to-low dose factor (250 000 for T25 as a PoD) is considered sufficiently conservative to cover for these differences.[83] Given this, the DMEL for aniline should be corrected. Applying a factor 4 to aniline instead of 10 results in a DMEL of 4.6 x 10^{-5} mg/kg bw/day, which compares well to the DMEL for o-anisidine (4 x 10^{-5} mg/kg bw/day).

Taking into account the discussion above, RAC proposes to carry forward to the risk characterisation of PAAs a **DMEL value of 4 x 10^{-5} mg/kg bw per day**.

Hazard assessment of azo colourants

Azo colourants used in tattoo inks are considered to be insoluble in water and are deposited in the derma as microcrystalline grains. Nevertheless, an equilibrium will always to some extent exist between the solid phase and small amounts of colourants dissolved in the lymph fluid constantly circulating in the body. Therefore, dissolved azo colourant molecules might be released into the skin or become systemically available, and it cannot be excluded that dissolved azo colourant molecules may be metabolically decomposed in the skin or in the liver.

Azo colourants are of low acute toxicity (Bafana et al., 2011), and most of them do not have harmonised classification. Nevertheless, some of them are classified for carcinogenicity and skin sensitisation, and, as already mentioned in the previous section (*Hazard assessment of PAAs*), some of them may decompose to PAAs of concern, either by ultraviolet (sunlight or laser light), enzymatic or bacterial degradation[84].

All azo colourants classified for health hazards considered relevant for tattooing (i.e. carcinogenicity, mutagenicity, reproductive toxicity, skin sensitisation, corrosion or significant irritation of skin or eye), as well as those covered by CPR (Annex II and Annex IV) and CoE ResAP(2008) (Table 2), are in the scope of this restriction proposal.

In addition, the Dossier Submitter proposed to include in the scope **azo colourants** that:

- could decompose via amide hydrolysis into PAAs with carcinogenic, mutagenic or skin sensitising properties (21 out of the 67 azo colourants with information that they can be found in tattoo inks, JRC, 2015b); or
- are based on 3,3'-dichlorobenzidine, and could form 3,3'-dichlorobenzidine during photo-decomposition (7 out of 67 analysed azo colourants); or
- have a scientific evaluation by Scientific Committee on Consumer Products (SCCP, now Scientific Committee on Consumer Safety, SCCS), stating that they may release one or more carcinogenic aromatic amines (4 azo colourants).

In tattoo inks found on the EU market (JRC, 2015b), a high prevalence of PAAs which are

[83] ECHA Guidance, Chapter R.8: "In contrast to threshold effects, no assessment factor is to be applied for this extrapolation step for non-threshold effects. The reason for this approach is that the linear model used for high to low dose extrapolation (see part on high to low dose extrapolation below), which is over about four orders of magnitude, is considered sufficiently conservative to also cover these differences in intraspecies sensitivity."

[84] Colourants used in tattoo inks are generally not produced for the purpose of tattooing, but for applications (e.g. paints for textiles, cars and plastics) for which sterility is not necessarily required. Therefore, biological degradation and PAAs formation can happen during storage (DEPA, 2017c).

formed partly or only by amide hydrolysis, and a low prevalence of PAAs formed only by azo bond cleavage was observed. Therefore, the Dossier Submitter proposed amide hydrolysis as the dominant decomposition mechanism for azo colourants presently used in tattoo inks, and, proposed to include in the scope of the restriction the specific azo colourants used in tattoo inks which can decompose to PAAs of concern via amide hydrolysis.

RAC points out that there is a high uncertainty related to the prediction of azo colourant decomposition mechanisms (further discussed in the section B.1.2.4), which could lead to both underestimation and overestimation of risk. RAC is of the opinion that these uncertainties cannot be reduced in the near future due to lack of information on the issues raised, but stresses that a relevance of azo bond cleavage cannot be ruled out and should be further explored if the restriction is updated.

Regarding photo-decomposition of azo colourants, an *in vitro* study on 11 azo colourants (Hauri & Hohl, 2015) showed that, in addition to PAAs as potential products of amide hydrolysis, azo colourants based on 3,3'-dichlorobenzidine degraded under UV light to 3,3'-dichlorobenzidine by azo bond cleavage. The result was not confirmed by *in vivo* study in a model of tattooed mice. However, as the authors hypothesised, this could be due to temporary formation of PAAs which quickly disappeared "either by on-site metabolism, additional photochemistry or by dissemination in the body", or "other products could have been generated or the decomposition products could have reacted with tissue and could not be extracted" (Engel et al., 2010). Since a general conclusion for other azo colourants is difficult to draw based on one study with limited number of substances tested (Hauri and Hohl, 2015), RAC supports the Dossier Submitter proposal to include in the scope azo colourants based on 3,3'-dichlorobenzidine (8 out of 67 azo colourants identified in tattoo inks on the EU market).

RAC also agrees with the Dossier Submitter's proposal to include 16 azo colourants listed in table 2 of the CoE ResAP(2008)1 into the scope, although the majority of them do not have harmonised classification relevant for this restriction proposal (primarily due to lack of sufficient data for evaluation), and none of them are registered under REACH. RAC is of the opinion that this approach is agreeable to not contradict national or international regulations, and responds to uncertainties caused by lack of sufficient data to exclude decomposition products that have, for example carcinogenic or mutagenic hazardous properties. If evidence that the azo colourants do not decompose as suggested is provided in the future, then this approach can be re-evaluated in the restriction's updates.

Substances considered to be impurities in tattoo inks, listed in table 3 of the CoE ResAP(2008) - semi-quantitative assessment

In Table 3 of CoE ResAP(2008)1, maximum allowed concentrations are set for 14 substances and one group of substances (13 elements, benzene-a-pyrene, and polycyclic aromatic hydrocarbons (PAHs)), considered as impurities in tattoo inks.

The Dossier Submitter has assessed individually some of these substances to determine the need for risk-based concentration limits in tattoo inks. Five substances (elements) stated below have been assessed to reflect the conclusions of recent risk assessments and due to their presence in some tattoo inks colours. For the remaining substances, except PAHs and nickel, the same CLs as in the Table 3 of CoE ResAP(2008)1 are proposed as technically

achievable limits.

Hazard and risk assessment of PAHs is described in the sections referring to carcinogenic substances.

Hazard and risk assessment for the five elements (arsenic, barium, copper, lead and zinc) is described separately for those assessed by a semi-quantitative approach (lead and arsenic), and for those assessed by a quantitative approach (barium, copper and zinc).

Lead

The critical health effects of lead include the effects on the nervous, haematopoietic and reproductive systems, and the carcinogenic effect. It should be noted that the mode of action for the carcinogenic effect is not completely understood and that tumours have only been seen at relatively high doses. The carcinogenic effect of lead is therefore, not considered as a critical effect in relation to tattooing.

The most critical effect of lead at low concentrations was considered to be the effects on the developing nervous system. It is still discussed whether there is a threshold for these effects. Therefore, a NOAEL or LOAEL for the most critical effect could not be established. This approach was confirmed by RAC in their opinions on Lead in PVC and Lead in shot used over wetlands where additional information from industry that lead was a threshold substance was not supported.

Lead is listed in Table 3 in the CoE ResAP(2008)1 (a list of maximum allowed concentrations of impurities in products for tattoos), and it has been detected in tattoo inks at levels exceeding the concentration limit stated in that table of 2 ppm (0.0002%).

Lead compounds have been included in the scope of this restriction because of their non-threshold reproductive toxicity effects (EFSA's CONTAM Panel (EFSA 2013)). These effects were acknowledged by RAC in the lead in jewellery and consumer product restrictions, in which it was concluded that there is no evidence for a threshold for a number of critical endpoints including developmental neurotoxicity (including from *in utero* exposure), increases in systolic blood pressure and renal effects (e.g., changes in proteinuria, glomerular filtration rate (GFR) or creatinine levels and clearance) (see Annex B.5.9 for more detail).

Based on data and analyses published on 22 March 2013 in the opinion of EFSA Panel on Contaminants in the Food Chain (CONTAM) (EFSA Journal 2010; 8(4):1570 (re-edited) there are three adverse effects of lead (neurodevelopmental, nephrotoxic and effects on developing foetuses) which can be considered for derivation of DMEL for lead:

a) the decrease of (full scale) IQ as intellectual deficit in children at ages 4 and higher as the critical endpoint for neurodevelopmental effects

The benchmark response selected for this endpoint was a 1 % change in full scale IQ score, i.e. a decrease in IQ by 1 point on the full scale IQ score. For changes in full scale IQ score a BMDL01 value of 12 µg/L was derived from the B-Pb levels in 6 year old children, which corresponds to an exposure of 0.50 µg/kg b.w. per day. No threshold could be identified for an effect of lead on IQ score and the magnitude of the effect was proportionately greater at lower B-Pb levels. The CONTAM Panel therefore concluded that a margin of exposure of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically

significant effect on IQ. This EFSA BMDL (01) value of 0.5 mg Pb/kg bw/d divided by a Margin of Exposure (MoE) of 10 has been used by RAC in the opinion on restrictions on lead and lead compounds in jewellery (ECHA, 2011b) to derive a practical exposure limit (DMEL) for children of 0.05 mg Pb/kg bw/d. Margin of Exposure (MoE) according to EFSA is a ratio of the dose at which a small but measurable adverse effect is first observed (BMDL (01) value (0.5 mg Pb/kg bw/d) and the level of exposure to the substance considered as not causing appreciable risk of a clinically significant effect. The same DMEL of 0.05 mg Pb/kg bw/d has been proposed by Dossier Submitter of this restriction to calculate a concentration limit of lead in tattoo inks.

b) nephrotoxic effects

The benchmark response selected for this endpoint was a 10 % change in the prevalence of Chronic kidney disease (CKD), defined as a Glomerular filtration rate (GFR) below 60mL/1.73 m2 body surface/min. A 10 % response was selected for the BMR as such a change was within the range of observable values and could have significant consequences for human health on a population basis (EFSA, 2009). For renal effects in adults, the BMDL10 of 15 µg/L based on B-Pb levels corresponds to a dietary lead exposure of 0.63 µg/kg b.w. per day. The CONTAM Panel concluded that a margin of exposure of 10 or greater would be sufficient to ensure that there was no appreciable risk of a clinically significant change in the prevalence of CKD. Therefore DMEL for prevention of nephrotoxic effects in adults would amount 0.63 µg/kg b.w. per day/10 = 0.063 µg/kg b.w. per day, thus only slightly higher than DMEL calculated for prevention of neurobehavioral effects in children.

c) effects on developing foetuses

Women of 20 to 40 years of age were used as a proxy for pregnant women, for whom specific consumption data were not available. Dietary exposure to lead in this group is in the range of 0.38 to 1.28 µg/kg b.w. per day for average consumers and 0.68 to 2.60 µg/kg b.w. per day for high consumers (lower bound for country with lowest average exposure – upper bound for country with highest average exposure). Exposure is therefore no greater than in the adult population overall. The relative sensitivity of the foetus to the effects of lead on neurodevelopment is not known. The CONTAM Panel therefore made the assumption that the developing foetus is as least as sensitive to this effect of lead as a young child.

Given that the foetal/maternal cord B-Pb concentration ratio is approximately 0.9, the maternal B-Pb level corresponding to the BMDL01 for effects on neurodevelopment (12 µg/L) is 13 µg/L, which is equivalent to a dietary exposure of 0.54 µg/kg bw per day. Using MoE of 10 would lead to derivation of DMEL 0.054 µg/kg b.w. per day to be used for prevention of potential lead effects in foetuses.

The non-threshold critical effect of developmental neurotoxicity for lead is seem to be the most sensitive effects, although the nephrotoxic effect in adults or potential effect on developing foetuses provides very close values of DMELs (0.05 – 0.063 µg/kg b.w. per day). Therefore RAC considers that a value of 0.05 µg/kg bw/day is appropriate for use as a DMEL in the risk characterisation, as proposed by the Dossier Submitter.

Arsenic

Arsenic is listed in Table 3 in the CoE ResAP(2008)1 as an impurity with maximum allowed concentration of 2 ppm (0.0002%) in tattoo inks. Arsenic compounds are also included in the

list of substances prohibited in cosmetic products under Annex II of the CPR. Historically, arsenic compounds have been used in pigments, e.g. red and yellow, but today they are present in tattoo inks probably only as impurities, at concentrations generally below 1 ppm but occasionally detected at higher levels, e.g. up to 60 ppm. The Dossier Submitter considered that in the context of the current knowledge about arsenic's health hazards and exposure via tattoo inks, there is a need to revisit the concentration limit in ResAP(2008)1.

The Dossier Submitter based their evaluation on the RAC opinions establishing a reference dose response relationship for carcinogenicity of inorganic arsenic compounds (in the framework of authorisation process)[85] and on the evaluation of the occupational exposure limits (OELS) for arsenic acid and its inorganic salts, particularly with reference to its carcinogenicity.[86]

As summarised in the RAC opinion (ECHA, 2017), arsenic can induce variety of toxic effects, including carcinogenicity (with the strongest evidence for lung, urinary bladder, kidney and skin) as well as non-carcinogenic dermal, gastrointestinal, haematological, cardiovascular, respiratory, reproductive and nervous system effects. Arsenic compounds do not react directly with the DNA, but are able to induce chromosomal alterations by DNA damage and interference with the DNA repair (WHO/FAO 2011). Inorganic arsenic is, therefore, proposed to be a threshold carcinogen (WHO/FAO 2011; Cohen et al. 2016). However, the available human and animal data do not allow the numerical identification of such threshold (ECHA, 2017; WHO/FAO 2011). There are indications that carcinogenic effects of arsenic could be present at very low doses, even at or below the maximum allowable concentration in drinking water (10 µg/L) recommended by the World Health Organization (WHO) (e.g. Kurttio et al., 1999; Mendez et al., 2017; Roh et al., 2017).

RAC agrees with the Dossier Submitter to consider carcinogenicity as the most sensitive outcome. Arsenic and inorganic arsenic compounds are classified as IARC Group 1 carcinogens, and two arsenic species registered under REACH in the largest quantities, arsenic acid and diarsenic trioxide, both have carcinogenicity identified as the most sensitive endpoint used in derivation of a DNEL/DMEL.

In the RAC opinion (ECHA, 2013), dose responses for arsenic carcinogenicity were derived for inhalation, oral and dermal route. The Dossier Submitter used in the assessment only the oral route, since the inhalation and dermal route were not considered relevant for intradermal application of tattoo inks. The RAC assessment for oral route was based on WHO/FAO (2011) assessment[87], and among the models with a good fit to the data, the linear model was chosen

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[85] ECHA, 2013. Application for authorisation – establishing a reference dose-response relationship for carcinogenicity of inorganic arsenic compounds, s.l.: ECHA risk assessment committee RAC/27/2013/07 Rev.1.

[86] ECHA, 2017. Committee for Risk Assessment (RAC) opinion on arsenic acid and its inorganic salts (29 May 2017), s.l.: European Chemicals Agency

[87] Based on lung and urinary bladder cancer data from prospective study in population exposed to arsenic in drinking water in north-eastern Taiwan), in which a $BMLD_{0.5}$ of 3 µg As/kg/day was derived (the benchmark dose lower confidence limit, resulting in 0.5% increase in lung cancer). WHO/FAO risk assessment was used by RAC since "the assessment was well described and used a variety models to find the best fit to the data from a number of studies, in order to find the most conservative cancer risk estimates using the defined approach".

for dose-response curve for lung tumours in humans exposed via drinking water:

excess lifetime lung cancer mortality risk = 1.7 x 10^{-3} per µg As/kg bw/day.

Since in the above mentioned prospective study only total arsenic was measured (without speciation), the risk assessment presented in the RAC opinion (ECHA, 2013) is "considered to apply to all forms of inorganic arsenic, in the absence of data to the contrary".

Uncertainties of the assessment are related to linear simplification of the dose-response curve for arsenic carcinogenicity and the unknown pattern of inorganic and organic arsenic species and compounds found in groundwater compared to those present in tattoo inks. They are further discussed in the section *B.1.2.4. Uncertainties in the risk characterisation*.

Taking into account the above stated uncertainties, RAC agrees with the Dossier Submitter's approach: to base the hazard assessment on previous RAC opinions (ECHA, 2013; ECHA, 2017), i.e. to choose carcinogenicity as the most sensitive outcome, and to apply linear dose-response curve for lung tumours, based on human data following oral exposure to arsenic in drinking water.

3. Substances with assumed threshold health hazard

For this group of substances health risk was evaluated in a quantitative manner with derivation of DNELs (methanol, reproductive toxicants with harmonised classification Repr. Repr. 1A/B and 2 (Annex B.5.9 and Appendix B.3), and certain substances considered to be impurities in tattoo inks (such as barium, copper and zinc), listed in table 3 of the CoE ResAP(2008)).

Methanol

Methanol was proposed to be included in the scope of the restriction due to its harmonised classification as STOT SE 1, based on its effects on the optic nerve and central nervous system (CNS) observed after a single exposure. It was chosen to be assessed by the Dossier Submitter as the only substance with STOT SE classifications found to be present in tattoo inks and not covered by other group or individual assessments.

A quantitative approach was applied, with DNEL derivation based on occupational exposure level of 260 mg/m^3 (or 200 ppm) for an 8 hour exposure, giving an exposure of 2.6 g/person/day, equivalent to 40 mg/kg bw/day. This is in line with the principles in ECHA Guidance R.8 (Appendix R.8-13, Deriving DNELs when community/national Occupational Exposure Limit (OEL) is available). The Dossier Submitter applied assessment factor of 5 in order to take into account possible higher sensitivities and longer exposure duration for the general population compared to workers, and derived a **DNEL of 8 mg/kg bw/day**.

The Dossier Submitter opted for the above described approach rather than for RAC-derived DNEL of 88 mg/kg bw/day (Annex XV dossier proposing restrictions on Methanol, 2015), since the OEL-based DNEL is more conservative. For the RAC-derived DNEL severe ocular toxicity was chosen as a point of departure, while the above stated OEL (260 mg/m^3) aims to protect workers from acute systemic and local irritation effects of methanol inhalation and is considered to be, in the majority of cases, also protective from very slight, sub-clinical CNS effects (FIOH 2008). Namely, neuropsychological effects of methanol inhalation have been

reported to start to appear at 270 mg/m^3 (discrete changes observed in tests on information processing, psychomotor skills, memory and concentration; Chuwers, et al. 1995; Cook, et al. 1991). Additionally, the Dossier Submitter considered that compared to the oral route, the inhalation route is more appropriate to represent methanol absorption through the skin. RAC agrees with the Dossier Submitter's approach and the derived DNEL value.

Substances classified for reproductive toxicity

In order to determine the risk from reprotoxic substances, the Dossier Submitter has assessed those reprotoxic substances which have harmonised classification as reproductive toxicants category 1 and 2, but which are not simultaneously classified as carcinogenic or mutagenic or skin sensitising substances. These "reprotoxic only" substances (34 in total) shown in table 9 in Annex B.5.9 of the Background document. So far only four of such substances, have been found in tattoo inks: bis(2-ethylhexyl) phthalate, dibutyl phthalate, mercury and disodium tetraborate, anhydrous (JRC, 2015b). For other reprotoxic compounds no information is available on their content in tattoo inks as an ingredient or impurity.

RAC supports the Dossier Submitter's statement that substances classified for reproductive toxicity in hazard category repro 1A/B due to their effects on sexual function and fertility in adults and developmental toxicity in offspring may exert their adverse effects when tattoo inks containing them are injected into dermis or other parts of the body (e.g. submucosal, intraocular, or under the tongue) of consumers. RAC considered that it is appropriate as proposed by the Dossier Submitter to use a quantitative hazard assessment approach to demonstrate a risk and to derive concentration limits for substances toxic to reproduction in tattoo inks for currently known repro 1A/B-classified substances.

Traditionally, reprotoxic substances have been assumed to have an individual threshold level below which no adverse effect is expected, thus a quantitative hazard assessment approach was used to derive DNELs for the "reprotoxic only" substances in accordance with ECHA guidance R.8 (ECHA, 2012). In line with this, dose descriptors (NOAEL/LOAEL) were identified from available studies and DNELs were calculated (see table 15 Overview of critical DNELs for substances toxic to reproduction in the Background document). Some of the substances that were assessed are known to have endocrine disrupting properties, e.g., phthalates. However, the Dossier Submitter still assessed reproductive toxicity as a threshold endpoint in this restriction proposal as this will indicate a minimum level of risk while the concern may be higher if there was no threshold due to any ED effects.

The dose-descriptors (i.e. NOAELs, LOAELs for sexual function and fertility, or development) for the "reprotoxic only" substances were in the range of 0.04-200 mg/kg/d (see table 10 of the Annex B.5.9 of the Background document. In addition, an exceptionally low dose-descriptor for tributyltin compounds of 0.00017 - 0.001 mg/kg/d was considered to be highly uncertain and not carried forward in the risk assessment of reprotoxic substances.

Overall, for 27 of the 34 substances, $DNEL_{\text{general population, reproductive effects}}$ could be derived (see Table 15 of the Annex B.5.14 of the Background document. For 96% of the substances DNEL values between 0.001 and 1 mg/kg bw/d were obtained (for a detailed description of derivation of DNEL(s)/, see Annex B.5.14 pp. 45-52 and Appendix B.3 pp. 109 – 229 of the

Background document).

The "reprotoxic only" substances were considered as a group, and the lowest DNEL for this group (not including the outlier) was carried forward by the Dossier Submitter to the risk characterisation, i.e. the most sensitive DNEL identified among the known 34 members of reprotoxic "only" compounds were considered to be representative for reprotoxic substances classified as Repr. 1 A/B. The overall $DNEL_{general\ population,\ reproductive\ effects}$ of 0.001 mg/kg bw/d is proposed by the Dossier Submitter as the most sensitive DNEL for risk assessment of reprotoxic substances (warfarin) in tattoo inks. RAC notes that among identified reprotoxic "only" substances identified by the Dossier submitter there are also other potent reprotoxicants such as 4-tert-butylbenzoic acid with DNEL of 0.0027 mg/kg bw/d or salts and esters of dinoseb with DNEL of 0.0033 mg/kg bw/d. Their DNEL is lower than that estimated by Dossier Submitter for dibutyl phthalate (DBP), with the lowest LOAEL out of the substances known to have been detected in tattoo inks. This comparison indicate on the possibility of occurring in tattoo inks the other potent reprotoxicants which were not yet identified.

The overall $DNEL_{general\ population,\ reproductive\ effects}$ of 0.001 mg/kg bw/d was derived by Dossier Submitter for the substances (R)- and (S)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrones (warfarin) based on a LOAEL of 0.04 mg/kg bw/d and an overall AF of 30. (See Appendix B.3 pp. 109 – 229 of the Background document). Both substances are listed in Annex VI of the CLP legislation as: Repr. 1A; H360D and are R- and S-enantiomers of the anticoagulant and rodenticide warfarin. The key studies and respective dose levels for the endpoint reproductive toxicity of Warfarin as shown in Table 73 and Table 74 of Appendix B.3 were selected based on the recent RAC opinion on a CLH report (Pesticide Registration and Control Division, 2012; RAC, 2014a). For the present restriction proposal a recent literature survey was performed from 2011 to now, as the CLH report on Warfarin was published in 2012. Doses of 2.5 mg/day (0.04 mg/kg bw/day, human female bodyweight of 60kg) have been reported to result in nasal hypoplasia and vertebral stippling in human offspring. Higher doses have resulted in a high percentage of embryofoetal mortality. (A NOAEL cannot be set and the value of 0.04 mg/kg bw/day represents a LOAEL which in turn approximates to an ED10 value). This value has been used in setting the specific concentration limits for reproductive toxicity of warfarin: 0.003% (RAC 2014a). Therefore, this dose level (0.04 mg/kg bw/day) is used by Dossier Submitter as POD in the current restriction proposal to derive the DNEL. Assessment factors were selected by RAC based on the Guidance on information requirements and chemical safety assessment Chapter R.8 (interspecies-remaining difference: 1, allometric scaling: 1, AF for intraspecies differences: 10, LOAEL instead of NOAEL: 3 with resulting overall AF 30 and DNEL 0.001 mg/kg/d).

RAC notes that (R)- and (S)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrones (warfarin) have not so far been detected in tattoo inks, therefore dibutyl phthalate (DBP), with the lowest LOAEL out of the substances known to have been detected in tattoo inks, is also considered for DNEL derivation to be used for assessment of risk to reproductive substances. (See Appendix B.3 pp. 139 – 143 of the Background document).

The study by Lee et al. (2004; cited in EU RAR) with dibutyl phthalate (DBP) was considered to represent the most relevant study regarding reproductive toxicity of 1,2-

benzenedicarboxylic acid, dihexyl ester, branched and linear using a grouping approach for seven phthalates (RAC, 2013b). The observed adverse effects are considered relevant for humans and the LOAEL of 2 mg/kg bw/d was selected as starting point (POD) for risk assessment. Human data which allow determining a human "no effect level" for 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear are currently not available. RAC has proposed this LOAEL as POD in their most recent opinion on DBP (RAC/24/2013/09 rev. 2; Helsinki, 12 April 2013). EFSA took the same study and LOAEL at the basis for deriving the TDI for DBP. Assessment factors were selected based on the Guidance on information requirements and chemical safety assessment Chapter R.8: AF for interspecies differences: 10; AF for intraspecies differences: 10; AF due LOAEL instead of NOAEL: 3. This leads to a value of DNEL for dibutyl phthalate (DBP) equal to: 2 mg/kg bw/d /300 = 0.00666 ≈ DNEL of 0.007 mg/kg/d as established previously (RAC/24/2013/09 rev. 2; Helsinki, 12 April 2013).

Considering further an issue of one Point of Departure (PoD) which could be used for assessment of risk posed by all reproductive toxicants which could be found in tattoo inks RAC notes that among reprotoxic "only" substances identified by the Dossier Submitter there are also other potent reprotoxicants such as 4-tert-butylbenzoic acid with DNEL of 0.0027 mg/kg bw/d or salts and esters of dinoseb with DNEL of 0.0033 mg/kg bw/d. Their DNEL is lower than that estimated for dibutyl phthalate (DBP). This comparison indicate on the possibility of occurring in tattoo inks the reprotoxicants more potent than dibutyl phthalate (DBP), which were not yet identified. Comparison of the potency of substances toxic to reproduction (Muller et al., 2012) demonstrated that the potency of developmental toxicants as expressed by their LOAEL varies between 0.002 and 2281 mg/kg bw/day indicating a potency range of up to 1 000 000. The potency of substances affecting fertility as expressed by their LOAEL differs by a factor of over 8 000. Therefore, RAC considers that an additional uncertainty factor of 10 should be applied to DNEL for DBP to set a point of departure which could be used as a surrogate DNEL for all reproductive substances in tattoo inks. This uncertainty factor takes into account huge variation in potency of substances toxic to reproduction, but also possibility of combined effects of several reprotoxicants with the same mode of action (some of which with endocrine effects) which might be present in tattoo inks.

$$\text{Surrogate DNEL}_{reprs} = 0.007 \text{ mg/kg/d}/10 = 0.0007 \text{ mg/kg/d}$$

The substances classified as category repro 2 in Annex VI of CLP have not been assessed individually due to the lack of available information and thus, the difficulty to estimate any dose descriptors. However, the Dossier Submitter proposed CL for Cat 2 10 times higher than for Cat 1. This is in line with the ratio between the GCLs for Cat 1 and Cat 2 in the CLP.

Substances considered to be impurities in tattoo inks listed in table 3 of the CoE ResAP(2008) – quantitative assessment

Barium

Barium sulphate is used in the flocculation of organic pigments to optimise their dispersibility, as a white colour, in other colours to adjust colour strength (because of its lightening effect), and as a filler in the production of lakes (JRC, 2015b).

Barium sulphate has very low solubility in most of the solvents, including water and lipids,

and thus, is relatively inert, but it can contain free soluble barium compounds as impurities (e.g. barium chloride, nitrate, and hydroxide). From soluble barium compounds, toxic barium ion can be released in the body.

Barium salts are restricted by CPR as well (in Annex II).

Concentration limit for barium, as an impurity in tattoo inks, set by CoE ResAP(2008)1 is 50 ppm (50 mg/kg). EU market surveillance showed that 20% of tattoo ink samples had Ba levels higher than the recommended CoE limit value (up to 17 737 mg/kg), although it has to be noted that the reported values refer to total barium content; the concentration of soluble barium in the samples is not known[88] (JRC, 2015b). The information on which basis the CoE ResAP(2008)1 limit was set is not available.

The Dossier Submitter, therefore, considered that the concentration limit set by the CoE ResAP(2008)1 for barium impurities should be revisited in the context of current knowledge about the hazards of barium compounds and of potential exposure via tattoo inks. The Dossier Submitter evaluated the available toxicological data (from ECHA registration dossiers and database searches) for the barium pigments/compounds found in tattoo inks with reference to the JRC report (Table 114 in the Background Document).

Soluble barium compounds

The hazard assessment of soluble barium compounds was based on barium chloride dihydrate, a barium salt readily soluble in water, for which toxicological data were available (a read-across approach).

The toxicity of barium compounds depends on their solubility and soluble Ba^{2+} salts are lethal at high concentrations (the LD_{50} values for barium chloride in rats range from 132 to 277 mg Ba/kg bw, and death has been reported in a number of human cases of accidental or intentional ingestion of soluble barium salts; ATSDR, 2007b). Namely, ionic barium, which can be released from soluble barium salts, is toxic to several organs and tissues, primarily muscles, cardiovascular system and kidney. In humans, characteristically marked hypokalaemia is observed (due to sequestering of potassium by muscle cells), and stimulation of striated, smooth and cardiac muscle results in violent peristalsis, arterial hypertension and arrhythmias (POISINDEX, 2018).

Human[89] and animal data do not indicate carcinogenicity, genotoxicity, reproductive toxicity, skin sensitisation, or skin or eye irritation potential of barium chloride and barium carbonate.[90]

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[88] There is a lack of a quantitative method for the soluble fraction of barium (JRC, 2015a, 2015b). Some of the barium substances found in tattoo inks are probably released due to the analytical method used for the analyses of the tattoo inks. It is considered, therefore, that used analytical methods do not reveal forms of barium actually present in the analysed tattoo inks (DEPA, 2012a).

[89] There is a case report on systemic poisoning in a 62-year-old man who sustained a barium chloride burn after his jackhammer penetrated a pocket of molten barium chloride (Stewart and Hummel, 1984). Nevertheless, dermal lesions (burns) were considered to be rather related to thermal burns than to chemical effect of barium chloride.

[90] However, barium nitrate causes serious eye irritation, and barium oxide and barium hydroxide are skin and eye corrosives according to the classification provided by companies to ECHA in REACH

Besides acute toxicity (i.e. lethality), the most sensitive endpoint in animal experiments was shown to be repeated dose toxicity with the effects primarily observed in the kidneys (kidney lesions), followed by cardiovascular system toxicity (increased systolic blood pressure). Although the health effects of acute barium poisoning are well described in humans, studies in humans have too many limitations in their study design to allow the derivation of a meaningful reference value for chronic exposure (small population size, short exposure regimen, difficulties in identifying barium exposure in the study population, inadequate control for important confounders). In a majority of the studies a LOAEL could not be found (ATSDR, 2007).

The Dossier Submitter therefore based its DNEL calculation on kidney effects of barium observed in NTP studies in rats and mice (NTP, 1994):

- Dietz et al. (1992) 13-week study in rats (part of NTP report), in which the lowest NOAEL was 61.1 mg Ba/kg bw/day in male rats (2000 ppm barium chloride dihydrate)[91], with LOAEL of 4000 ppm barium chloride dihydrate, at which kidney lesions (tubular dilatation) were observed, as well as some other toxic effects (decreased body weight gain, elevated phosphorous levels, neurobehavioral effects, lymphoid depletion in spleen and thymus). Applying an assessment factor (AF) of 100 (10 for inter-species and 10 for intra-species variation), DNEL of 0.61 mg Ba/kg bw/day was calculated.
- Reference dose of 0.6 mg/kg bw/day was derived by Dallas & Williams (2001), based on 60 mg Ba/kg bw/day as the most sensitive NOAEL from the range of NOAEL values found for renal effects of barium (60 to 90 mg Ba/kg bw/day) in chronic NTP studies in rats and mice (with AF of 100 applied);
- The derived updated intermediate and chronic duration oral minimal risk levels (MRLs) by ATSDR (ATSDR, 2007) were based on NTP 13-week study in rats (NOAEL of 65 mg Ba/kg bw/day, with LOAEL of 115 mg Ba/kg bw/day for increased kidney weights in female rats) and 2-year study in mice ($BMDL_{05}$ of 61 mg Ba/kg bw/day for a 5% increase in the incidence of nephropathy in male mice)[92].

The Dossier Submitter proposed a **DNEL of 0.60 mg Ba/kg bw/day** to be carried forward to the risk assessment of **soluble barium compounds**.

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registrations, and can cause irritation of the skin according to information provided in POISINDEX (2018). They do not have harmonised classification but it could be noted that proposed concentration limit of 0.84% for soluble barium salts is lower than GCL for skin irritants Cat. 1 (1%), skin corrosives Cat. 1 (5%), eye irritants Cat .1 (3%), and eye corrosives Cat. 1 (1%). These substances have not yet been detected in tattoo inks. Barium hydroxide is, besides industrial uses, used as a depilatory agent (IPCS, 1990).

[91] Expressed as the final (at the end of 13-week experiment) barium dose at 2000 ppm of barium chloride dihydrate in drinking water. This is a conservative estimation, since initial barium dose at 2000 ppm of barium chloride dihydrate in drinking water was 162.9 mg Ba/kg bw/day (according to Table 1 in Dietz et al., 1992).

[92] ATSDR calculated intermediate-duration and chronic-duration MRLs of 0.2 mg Ba/kg bw/day since in addition to default AF of 100, modifying factor of 3 was included to account for the lack of an adequate developmental toxicity study.

RAC agrees with this approach in general. Kidney effects were the most sensitive toxic effects of barium observed in two animal species, at very similar dose levels. Human data showed some indication of cardiovascular effects of chronic exposure to barium (Brenniman and Levi, 1984), but since the important confounders were not controlled for (e.g. the use of water softeners which would reduce exposure to barium and increase sodium levels, duration of exposure, actual barium intake via water and food), the study is not considered robust enough to derive a reliable DNEL.

Nevertheless, taking into account intradermal application of tattoo inks for which 100% absorption is proposed in the exposure scenario, RAC considers that PoD of 60 mg Ba/kg bw/day for renal effects of barium in rats should be corrected for percentage of oral uptake of barium chloride in rats. According to ATSDR (ATSDR, 2007b; Taylor et al., 1962), 7% of barium chloride was absorbed in adult, fed rats, after single oral dose (by gavage). Corrected PoD value is, therefore, approximately 4 mg Ba/kg bw/day, which leads to **DNEL of 0.04 mg Ba/kg bw/day**.

Insoluble barium compounds (i.e. barium sulphate)

The Dossier Submitter performed hazard and risk evaluation of insoluble barium salts by assessing information on barium sulphate ($BaSO_4$), as this is by far the most widely used insoluble barium salt (e.g. for medicinal purposes as a gastrointestinal contrast medium taken by mouth or rectally, as radiopaque substance added to bone cement or to subcutaneous hormonal implant). $BaSO_4$ is generally regarded as nontoxic due to its poor solubility, and is included in the List of colourants allowed in cosmetic products (CPR, Annex IV). However, it is of utmost importance that $BaSO_4$ is analysed for presence of soluble barium salts, as required for medical or cosmetic products.

Although $BaSO_4$ particles are not soluble in cellular membranes, they could be taken up into the cells by pinocytosis or phagocytosis, fused with lysosomes, and, under acid conditions (pH 4.5-5.0), may become soluble. However, it is still unclear in which cell types and at what rates this process could occur.

The hazard assessment, as presented in the relevant REACH registration dossier, was mainly done by read-across from soluble barium compound (barium chloride), as a worst-case situation. Therefore, carcinogenicity, genotoxicity, reproductive toxicity, skin sensitisation and skin or eye irritation/corrosion are not indicated for $BaSO_4$. The use of $BaSO_4$ in cosmetic products is allowed by Cosmetic Ingredient Review (CIR, 2014), at concentration of up to 0.99% and 37% in rinse-off and leave-on products, respectively, when formulated in absence of other irritants. Regarding repeated dose toxicity, the $BaSO_4$ REACH registrants obtained a DNEL of 13 000 mg/kg bw/day for the general population via oral route (systemic effects), applying an AF of 30, but the chosen study was not specified. Just for illustration, up to 321 g of barium sulphate (around 5000 mg/kg bw for 60 kg person) is a recommended as an oral dose for oesophagus, stomach, and duodenum radiographic studies in adults and children (12 years or older) (POISINDEX, 2018). However, data on the potential toxicity of intradermal (or intramuscular) application of barium sulphate are lacking.

RAC notes that hypersensitivity reactions (including severe reactions, such as anaphylaxis) have been reported in humans after oral and dermal administration of $BaSO_4$ preparations for diagnostic purposes (POISINDEX, 2018; DRUGDEX, 2018; Seymour and Kesack, 1997).

However, it is not clear whether barium sulphate itself or the additives in the barium suspension (e.g. methylparaben, carboxymethylcelluose, glucagon) are responsible for the observed adverse effects (DRUGDEX, 2018; Seymour and Kesack, 1997). Nevertheless, the incidence of severe hypersensitivity reactions is very low (approximately one case in 1 million patients following oral administration of barium sulphate suspension) (DRUGDEX, 2018). Regarding dermal reactions, Cosmetic Ingredient Review stated that "the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that barium salts do not have the potential to induce sensitisation" (CIR, 2014).

$BaSO_4$, due its insolubility in majority of solvents, is poorly absorbed from the gastrointestinal tract in humans and animals. Nevertheless, limited data show that small quantities could be dissolved in acidic gastric lumen and absorbed, both in humans (e.g. Clavel et al., 1987) and animals (e.g. McCauley and Washington, 1983; Konduru et al., 2014). Also, experiments in animals showed that $BaSO_4$ becomes systemically available after inhalation exposure (Konduru et al., 2014). Namely, after short-term inhalation exposure, $BaSO_4$ nanoparticles were rapidly and extensively cleared from the lungs (by 95% over 34 days, after 4-week exposure) (Konduru et al., 2014; Schwotzer et al., 2017). It is still unclear, however, how much ionic barium, i.e. dissolution of $BaSO_4$ particles, contributes to rapid clearance and translocation (Schwotzer et al., 2017). The soluble fraction of barium deposited in the lungs was below 5% of total lung burden (Schwotzer et al., 2017). Systemic toxicity in inhalation experiments (Konduru et al., 2014; Schwotzer et al., 2017) was not observed, since systemically available dose of barium was probably too low (Konduru et al., 2014)[93], which is probably also the case in baritosis (a benign pneumoconiosis in workers exposed to barium sulphate dust). Namely, systemic toxic effects of $BaSO_4$ were not observed in workers with baritosis, although presence of barium in regional lymph nodes has been detected (Dosios and Karydas, 2003), as well as a decline in barium lung burden, suggesting a decrease in the amount of accumulated barium in the lung and possible redistribution to extra-pulmonary tissues (US EPA Barium 2005).

Regarding local effects, they were studied in the lung tissue after inhalation exposure and in tissues surrounding application site of bone cement ($BaSO_4$ is used in bone cement as a radiopaque agent). Low grade lung tissue inflammation was noted after 90-day inhalation exposure to $BaSO_4$ nanoparticles (a slight increase of polymorphonuclear neutrophils in bronchoalveolar lavage fluid, which declined during post-exposure period). Histologically, accumulations of particle-laden macrophages in lung tissue and associated lymph nodes, very slight inflammatory cell infiltrations in the lungs, and intra-epithelial eosinophilic globules and mucus cell hyperplasia in the nasal cavity were described (Schwotzer et al., 2017). Apoptosis

[93] Exact data for systemic availability after short-term (28-day and 90-day) inhalation exposure are not available. Very rough estimate is <10 mg/kg of systemically available barium (with unknown percentage of dissolved, ionic barium) in 90-day inhalation exposure experiment (Konduru et al., 2014), according to 40% systemic availability of BaSO4 nanoparticles after intratracheal instillation (Konduru et al., 2014) (with considerable uncertainty due to the differences between intratracheal instillation and inhalation exposure route; Driscoll et al., 2000), inhalation volume of 15.7 L/h for female rats (according to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8), and body weight of 200 g for 7-week old female Wistar Han rats (according to NIH (2014) Historical Control Body Weights for All Routes/Vehicles, Wistar Han Rats).

in alveolar epithelial type II cells was not observed (Schwotzer et al., 2018).

It is well described that $BaSO_4$, as a contrast medium added to bone cement, escapes into the surrounding tissues due to mechanical wearing of the material (Rae., 1977; Acarturk et al., 2008; Shardlow et al., 2003). Data on $BaSO_4$ release rate from bone cement is limited. Based on experimental data with simulation of mechanical wearing process of $BaSO_4$-containing cement (10% of BaSO4) in knee arthroplasty during 3-6 months of use, it could be calculated that approximately 22 mg of barium is released from bone cement during 3-6 months, or 0.002-0.004 mg/kg bw/day (it is unknown, however, how much barium could become dissolved) (Mueller et al., 2017). Due to low amounts released and low water and lipid solubility of $BaSO_4$, systemic effects are unlikely to occur, as demonstrated by *in vivo* experiment in rabbits (Acarturk et al., 2008) and by the fact that $BaSO_4$ is presently still used as a bone cement radiopacifier in human and veterinary medicine (in concentrations reaching 35%). However, debris consisting of bone cement particles (mainly polymethylmethacrylate and additives, such as BaSO4 or other radiopaque marker, or antibiotics), induces inflammatory reaction when phagocytosed by macrophages, with consequent activation of (pre-)osteoclasts and osteolysis (Shardlow et al., 2003). In vitro experiments indicate that $BaSO_4$ in bone cement leads to greater induction of (pre)osteoclasts compared to bone cement without radiopaque substance (e.g. Sabokbar et al., 1997; Xu et al., 2005; Wang et al., 2005).

To summarise, according to information published to date, it is not likely that gradual release and intracellular dissolution of $BaSO_4$ from a tattoo pigment will be extensive and fast enough to lead to systemic toxicity similar to that induced by soluble barium salts. $BaSO_4$ applied as a pigment is not expected to rapidly migrate from tattooing site, taking into account its poor solubility in water and lipid media. On the other hand, results from *in vitro* study of $BaSO_4$ as radiopacifier in bone cement as well as from recent inhalation studies, indicate that $BaSO_4$ particles are capable of inducing local inflammatory response in exposed tissues. Question remains whether phagocytosed $BaSO_4$ could lead to inflammatory and granulomatous skin reactions in susceptible population. Although baritosis is a non-granulomatous (non-fibrotic) form of pneumoconiosis, barium granuloma of the colon and rectum has been observed as a rare complication of $BaSO_4$ application in radiological examination of the gastrointestinal tract in humans (Mayorga et al., 1992). Granulomatous reaction (of foreign body type) was described after injection of $BaSO_4$ in fat pads of guinea pigs (Goldner and Adams, 1977). However, no data on $BaSO_4$ kinetics of release from a tattoo pigment or dose response in relation to granulomatous reaction could be identified.

It should be pointed out that this type of reaction (foreign body granuloma, e.g. in papulo-nodular form) have been mainly associated with black pigments (carbon black), and the hypothesis, although rather uncertain, is that they originate from pigment overload (Serup et al., 2016). This type of reaction was not evaluated as a hazard in the restriction proposal due to inadequacy of available data.

Taking into account that there are presently no available relevant studies indicating CMR, skin sensitising or skin or eye irritation/corrosion hazards for $BaSO_4$ that would trigger its restriction in tattoo inks, RAC agrees with the Dossier Submitter's proposal not to restrict $BaSO_4$ in tattoo inks at the present moment. However, RAC points out the need to investigate further the factors, both substance- and host-related, responsible for non-specific

inflammatory and granulomatous reactions to tattoo inks.

The importance of granulomatous type of adverse reactions to tattoo inks has been also pointed out during the Public Consultation (comment #1928b).

Barium in azo colourants

According to the list of colourants allowed in cosmetic products (CPR Annex IV), a total of 17 entries could potentially contain barium but many of these entries are already captured by the inclusion in the scope of CPR Annex II and Annex IV substances.

The following barium pigments were found in tattoo inks on the EU market (JRC, 2015b) and were evaluated by the Dossier Submitter:

Table 14. Barium pigments found in tattoo inks

Azo colourant name	**Already regulated**	**Toxicity evaluation**
Pigment Red 53:1 barium bis[2-chloro-5-[(2-hydroxy-1-naphthyl)azo]toluene-4-sulphonate]	CPR Annex II CoE ResAP(2008)1, Table 2	Observed adverse effects (in the blood, spleen and liver) in toxicological studies seem unrelated to the contribution of Ba^{2+} ion[94], and are likely due to the organic moiety of this substance (either the parent azo dye and/or the azo cleavage products)
Pigment Red 49:1 barium bis[2-[(2-hydroxynaphthyl)azo]naphthalenesulphonate]	Not in CosIng database, but listed in CPR Annex IV (with condition: Maximum concentration in ready	Observed adverse effects (hemolysis, splenomegaly, hemosiderosis, bone marrow hyperplasia, increased urine bilirubin) in toxicological studies seem unrelated to the contribution of Ba^{2+} ion[95], and are likely due to the

[94] Since similar effects were not observed in NTP studies with barium chloride (NTP, 1994) at Ba^{2+} ion doses 10-20x higher in rats and mice, respectively.

[95] Since the effects were observed in animal studies with sodium salt of the pigment, which did not include exposure to Ba^{2+} ion.

	for use preparation 3%)	organic moiety of this substance
Pigment Red 48:1 barium 4-[(5-chloro-4-methyl-2-sulphonatophenyl)azo]-3-hydroxy-2-naphthoate	Not in CosIng database, but listed in CPR Annex IV (without conditions)	No DNEL could be derived due to lack of data (pigments used for read-across did not contain barium)
Pigment Red 57:2 barium 3-hydroxy-4-[(4-methyl-2-sulphonatophenyl)azo]-2-naphthoate	Not in CosIng database, but listed in CPR Annex IV (condition related to purity criteria)	No DNEL could be derived due to lack of data (pigments used for read-across did not contain barium)
Pigment Red 60:1 barium(2+) hydrogen 2-[(2-hydroxy-3,6-disulphonato-1-naphthyl)azo]benzoate	Not included in CPR Annex IV (thus not allowed in cosmetic products)	No DNEL could be derived due to lack of data (no toxicological information was identified for this pigment)
Pigment Red 51 barium bis[4-[(2-hydroxy-1-naphthyl)azo]-2-methyl benzenesulphonate]	CPR Annex IV (without conditions)	No DNEL could be derived due to lack of data (no toxicological information was identified for this pigment)

None of these colourants have a harmonised classification.

CPR Annex II: not allowed in cosmetic products

CPR Annex IV: lists of colourants allowed in cosmetic products (with or without specified conditions)

CoE ResAP(2008)1 Table 2: colourants which tattoo products should not contain

CosIng database: European Commission's Cosmetic Ingredient database - only colourants used in cosmetic products which are authorised in Annex IV to CPR (Cosmetic Regulation No 1223/2009) are listed in CosIng

RAC supports the justification for the Dossier Submitter's assumption that toxic effects observed for Pigment Red 53:1 and Pigment Red 49:1 are due to the parent azo colourant and/or the azo cleavage products, and are unrelated to barium ion (please see the footnotes linked to the Table above). For this reason and due to a lack of relevant data for other four evaluated colourants, RAC agrees with the Dossier Submitter not to perform derivation of a DNEL based on the barium moiety of the pigments.

Copper

Soluble copper

The CoE ResAP(2008)1, Table 3, recommends a maximum concentration of 25 ppm soluble copper (25 mg Cu/kg ink) in tattoo inks, although a definition of 'soluble' Cu in the context of tattoo inks is lacking. The reasoning behind the recommended limit value cannot be assessed since background papers are not available.

High concentrations of copper have been found in tattoo inks (up to 49 500 ppm according to JRC, 2015b report), but it is considered that this is most likely due to the use of green and blue pigments based on the copper ion (e.g. phthalocyanines). Although in the CoE ResAP(2008)1 only soluble copper is addressed, most of the analytical methods available

today are not capable of distinguishing between the soluble form and copper incorporated in colourants.

The Dossier Submitter based its evaluation of copper on the DEPA (2012) report with the addition of supplementary information:

- Copper (oxidation state zero) is not classified for health effects according to Annex VI of the CLP Regulation.
- Copper flakes (coated with aliphatic acid) has a harmonised classification as Eye Irrit. 2.
- Copper chloride is classified with Acute Tox. 4 (H302: Harmful if swallowed).
- Copper sulphate is classified with Acute Tox. 4 (H302: Harmful if swallowed), Skin Irrit. 2 (H315: Causes skin irritation) and Eye Irrit. 2 (H319: Causes serious eye irritation).
- RAC proposed no classification for granulated copper in its discussion on a harmonised classification proposal (Committee for Risk Assessment working document, 2018): "RAC concludes that in the absence of relevant data, no proposal for classification for eye irritation can be made for granulated copper."
- Copper (metallic) or copper compounds have not been evaluated by IARC.

Although copper is an essential element (for the function of many enzymes such as catalase and peroxidase; as an important catalyst for heme synthesis and iron absorption) with the recommended dietary allowance (RDA) of 0.900 mg/day (0.015 mg/kg for a 60 kg person) (Institute of Medicine US, 2001), it is toxic at higher doses. According to POISINDEX (2018) database[96], the lowest published toxic dose for humans via the oral route is 0.12 mg/kg, with nausea and vomiting reported, and the estimated lethal dose in an untreated adult is 10 to 20 g copper. The most prominent toxic effects include lesions in the gastrointestinal tract (e.g. gastrointestinal bleeding), haemolysis, hepatic and renal failure. Accidental subcutaneous injection of copper glycinate at high doses (e.g. 2.5 g copper) has resulted in severe local effects (necrosis) and systemic effects similar to oral exposure. Severe ocular damage may occur after penetration of the eye by fine copper-containing fragments.

In the evaluation of health hazards by exposure to copper in drinking water prepared for the DEPA (Nielsen, 1997), the critical effect in humans was considered to be local irritation in the gastrointestinal tract, but a NOAEL or LOAEL could not be established based on the available data. The only systemic effects reported were liver effects (liver cirrhosis) in young children, but it is considered that these cases are only partly (if at all) attributable to increased oral intake of copper. Various authors suggested that an inherited predisposition in conjunction with increased copper intake are responsible for observed toxic effects (Tanner, 1998; Sriramachari and Nayak, 2008; Nayak and Chitale, 2013).

[96] Poisindex® (Micromedex® Healthcare Series for Windows® Greenwood Village, CO: Truven Health Analytics Inc.), is a software database used by poison control centres all over the world. It has information on more than 400 000 chemical and household products to assist in the management of calls.

The Dossier Submitter chose to base a DNEL on the limit values for oral copper intake in populations with normal copper homeostasis, derived by the Scientific Committee on Food (SCF, 2003) and the World Health Organisation (WHO, 2004), considering them as reliable sources since their assessment is based on studies in humans:

- The Scientific Committee on Food (SCF, 2003) derived the Tolerable Upper Intake Level for Copper of 5 mg/day for adults (not applicable during pregnancy or lactation), and 4 mg/day for children older than 10 years. Limit values were based on data in adult humans (for children, extrapolation was done from adult limit value, based on relative body weight), with liver function as the critical endpoint.
- WHO set the guideline value of 2 mg Cu/L drinking water (equalling a mean total copper intake of 2.2 mg/day if assuming a body weight of 60 kg and a water intake of 1.1 L/day; US EPA, 2011), based on studies in adults and infants, with gastrointestinal and liver effects as the critical endpoints.

The Dossier Submitter did not consider animal data from one 90-day oral repeated dose toxicity study as relevant enough for DNEL derivation (at least not without in depth scrutiny), but pointed out that the DNEL value derived (0.041 mg/kg bw/day; REACH registration dossier for copper) is rather similar to the SCF Tolerable Upper Intake Level (4 mg/day, i.e. 0.067 mg/kg bw/day for a 60 kg person).

The Dossier Submitter also considered the irritative effects of copper. It was concluded that besides copper sulphate, which has a harmonised classification as skin and eye irritant Cat. 2 (and as such is already in the scope of the proposed restriction as a skin irritant), data for all other copper substances are extremely limited.

RAC notes that although copper metal and copper compounds have not been classified for skin sensitisation, there are reports in the literature of hypersensitivity reactions to copper. These are for example in women with copper intrauterine device (IUD) as a method of contraception[97] (Fage et al., 2014, review article), patients with copper-containing dental metal prosthesis (Vergara et al., 2004) or in persons occupationally exposed to copper coins (Suárez et al., 2002). Patients had a positive reaction to patch test with 1%, 2% or 5% copper sulphate, and symptoms disappeared after exposure ceased (Barranco, 1972; Rongioletti et al., 1985; Pujol et al., 1998). Fage et al. (2014) concluded that although "in a few and selected cases, copper can result in clinically relevant allergic reactions", "copper is a very weak sensitizer as compared with other metal compounds". A similar conclusion is provided in an earlier review report by Hostynek and Maibach (2004), who stated for copper that "in contrast to other metals such as nickel or chromium, reports of untoward reactions, systemic as well as cutaneous, are extremely rare".

Taking into account uncertainties related to skin irritation and sensitisation potential of copper, RAC agrees with the Dossier Submitter's proposal to derive a DNEL based on a tolerable daily intake (TDI) of 2.2 mg Cu/day, i.e. 0.037 mg Cu/kg bw/day, following WHO approach to provide an adequate margin of safety in populations with normal copper

[97] The copper used in copper-containing IUDs is quite pure, with very low content of nickel (Fage et al., 2014).

homeostasis. The WHO guideline value (which is same as in EU water directive, 2015) is based on a solid amount of human data, including studies in infants. Nevertheless, since copper absorption in human subjects from diets containing adequate levels of copper (1-10 mg/day) ranges from 30-60% in human subjects (EU RAR 2007), RAC proposes to correct derived DNEL value for 50%, obtaining **DNEL** value for intradermally applied copper of 1.1 mg Cu/day, or **0.019 mg Cu/kg bw/day**.

Regarding skin irritation, if new data for copper and its compounds justify harmonised classification for this hazard endpoint, these substances will be automatically in the scope of the restriction. The same reasoning applies for skin sensitisation.

Insoluble copper - phthalocyanines used as colourants

According to the JRC (JRC, 2015b), phthalocyanines are macrocyclic compounds having four pyrrole-like subunits linked to form a 16-membered ring in their structure forming coloured complexes with various metals. In the case of copper as the center metal, several intensely blue or green coloured complexes are formed.

Copper-phthalocyanines complexes are generally considered to be of very low solubility in most solvents, including water, i.e. they do not dissociate to the phthalocyanine anion and copper ions to a considerable degree. The same applies for other metal-phthalocyanines complexes (Liao and Scheiner, 2001).

The phthalocyanine Pigment Blue 15 (CAS No. 147-14-8) has been evaluated in the OECD SIDS program (OECD SIDS, 1997). Further, Pigment Blue 15 is reviewed in a REACH registration dossier (ECHA, 2017). In rats, a reduced number of red blood cells was observed after oral administration of the pigment colourant by gavage (1000 mg/kg bw) daily for 28 days. The NOAEL was tentatively established at 200 mg/kg bw per day (ECHA, 2009), however, the degree of red blood cells reduction was not provided, so adversity of red blood cells reduction cannot be assessed.

In the 28-day study, detailed data is not available (it is a Japanese study where only summary is in English). The haematological changes are described as slight. According to the Guidance on the application of the CLP criteria (ECHA, 2017a) (section 3.9.2.5.2), slight haematological changes which are not accompanied by any other adverse symptoms are considered not to be toxicologically relevant.

In rats and mice, no effects were seen after administration of the pigment (Pigment Blue, CAS no 147-14-8) in the feed (0.3 to 5%) for 90-days (ECHA, 1979).

Further, no tumours were observed in mice given the pigment subcutaneously for 8 months. No genotoxic effects were observed in a variety of tests.

In rats, no effects on fertility and no effects in offspring were observed after oral administration of the pigment by gavage (0, 40, 200, 1 000 mg/kg bw) daily for 42 days (males) and from 14 days before mating to 3 days after giving birth (females). A NOAEL was tentatively established at 1 000 mg/kg bw/day for offspring as well as for the parents.

The critical effect of phthalocyanine after repeated exposure over a prolonged time period is

considered to be the decreased number of red blood cells. However, in the 90-day study, doses up to 4 500 mg/kg bw/day were administered; no adverse treatment related effects were observed (neither macroscopically nor microscopically). Therefore, clinical chemistry parameters were not tested. It should also be noted that, the magnitude of the decrease in the number of red blood cells in exposed animals compared to controls is not presented. Therefore, it cannot be evaluated whether the decrease is statistically and biologically significantly different compared to the control group.

Thus, the available data do not allow any final conclusion on repeated dose toxicity. According to the limited data available, it appears that phthalocyanines do not possess toxic properties requiring classification as STOT RE, toxicity to reproduction, carcinogenicity or mutagenicity, although the data do not allow for a final conclusion.

Limited available data do not trigger phthalocyanines' classification for STOT RE, toxicity to reproduction, carcinogenicity or mutagenicity, and a derivation of a valid DNEL was thus judged by the Dossier Submitter not to be possible.

Although laser treatment of phthalocyanines has shown to form toxic degradation products (such as dicarbonitrile, benzonitrile, benzene, and hydrogen cyanide), there are presently too many knowledge gaps to allow hazards and risks assessment related to laser removal of these colourants. This issue should be further assessed in any review of the restriction if new information becomes available.

Zinc

Zinc oxide (ZnO; CAS no 1314-13-2; Pigment white 4; CI no 77947) is insoluble in water and is one of four white colourants (all being inorganic pigments) reported to be used in tattoo inks. The presence of zinc (Zn; CAS no 7440-66-6) and zinc ferrite brown spinel (CAS no 68187-51-9; Pigment Yellow 119; CI no 77496) in tattoo inks has also been reported (JRC, 2015b).

Zinc is listed in Table 3 in the CoE ResAP(2008)1 as an impurity with maximum allowed concentration of 50 ppm (mg/kg) in tattoo inks. Zinc oxide is included in the list of colourants allowed in cosmetic products (Annex IV, entry no 144) of the cosmetics regulation (EC No 1223/2009). It is also allowed as an UV filter in cosmetic products (Annex VI, entry 30 (non-nano) and 30a (nano)) with a maximum concentration in ready for use preparation of 25% for both forms (except in applications that may lead to exposure of the end-user's lungs by inhalation).

It is known that Zinc is an essential mineral for growth and development, testicular maturation, neurological function, wound healing and immune function. However, it has been demonstrated that zinc compounds may be hazardous to health in higher doses (the LD_{50} values of several zinc compounds range from 186 to 623 mg Zn/kg bw/day in rats and mice; ATSDR Zinc, 2005).

Local effects: As reviewed by the Dossier Submitter in the Background Document zinc compounds when applied on skin induce mild irritating effects and when applied to eye may induce ocular irritation.

Genotoxic effects: The weight of evidence from the *in vitro* and *in vivo* genotoxicity tests

supports the conclusion that zinc, notwithstanding some positive findings at chromosome levels at elevated doses, has no biologically relevant genotoxicity activity (Walsh, et al., 1994) (WHO, 2001).

Carcinogenic effects: There are no indications of carcinogenic effects of Zn in rodents after oral intake. However, for some of the animal studies on zinc and its inorganic compounds it was not possible to assess the carcinogenicity from the available studies (DFG, 2010).

In human studies, no indication of a significant increase in cancer mortality was found in a prospective mortality study of 4 802 workers in nine American copper and zinc refining plants (DFG, 2010). In a further study, the association between supplementary zinc intake and the occurrence of prostate cancer was investigated in 46 974 male US Americans. During the 14-year observation period, 2 901 new cases of prostate cancer were diagnosed, including 434 in an advanced stage. Approximately 25% of the participants took zinc supplements (24% up to 100 mg/day, 1% above 100 mg/day). Supplemental zinc intake of up to 100 mg/day was not associated with an increased prostate cancer risk. With high zinc intake (> 100 mg/day), the relative risk for advanced prostate cancer was 2.29 (95% CI: 1.06 to 4.95). However, the authors noted that residual confounders by supplemental calcium intake or unmeasured zinc supplement use cannot be excluded (DFG, 2010). Even, after taking into consideration the other studies reviewed in the Background Document by the Dossier Submitter, the evidence for carcinogenicity is still limited, which makes it difficult to conclude.

Reprotoxic effects: Zinc, at doses higher than naturally found in food, is suspected to cause reduction of fertility in rats. In the two-generation study (Khan et al., 2007) in which male and female rats were administered test material ($ZnCl_2$) at the doses of 7.50, 15 and 30 mg/kg/d over two successive generations the exposure of F0 and F1 parental rats to test material showed significant reduction in fertility, viability and the body weight of F1 and F2 pups from the high-dose group but caused no effects on litter size, weaning index, and sex ratio. Significant reduction in body weights of F0 and F1 parental males and postpartum dam weights female rats was observed. Reduction of brain, liver, kidney, spleen and seminal vesicles weights of males and in the spleen and uterus of females was observed in F0 and F1 rats. Gross lesions were observed in gastro-intestinal (GI) tract, lympho-reticular/ hematopoietic and reproductive tract in parental rats in both generations. Reduced body fat was also recorded in F1 parental rats (Khan, et al., 2007). The effects seen at 7.5 mg/kg bw/day, were considered to be biologically non-significant and therefore this exposure level was considered to be the NOAEL.

A study reported on ECHA's dissemination website (ECHA registration dossier, 1986c) showed that dietary zinc (Zn) supplementation at 4 000 ppm zinc as zinc sulphate, $ZnSO_4$ (4mg/kg/day) had reduced male fertility in rats under the conditions of the study.

Treatment of pregnant women with 20 mg of elemental zinc per day did not have adverse outcomes, including any effect on the birth weight of babies (Bingham et al., 2001).

Specific target organ toxicity: As reviewed in the Background Document, the repeated exposure of animals or humans to zinc compounds lead to hypocupraemia manifested as anaemia with low haemoglobin and haematocrit, or as reduced activities of erythrocyte superoxide dismutase. The ATSDR (Agency for Toxic Substances and Disease Registry) has derived an intermediate-duration oral MRL (Minimal Risk Levels) of 0.3 mg Zn/kg/day for zinc

based on decreased erythrocyte superoxide dismutase, a sensitive indicator of body copper status, and changes in serum ferritin in women given supplements containing zinc gluconate for 10 weeks (Yadrick, et al., 1989). The US EPA has derived an oral reference dose (RfD) of 0.3 mg/kg bw/day for zinc (Integrated Risk Information System (IRIS), 2005). The Opinion of the Scientific Committee on Food (SCF) on the Tolerable Upper Intake Level of Zinc (expressed on 5 March 2003) reported that high exposure to Zinc in humans, gives systemic toxicity after repeated exposure on the Cu-balance, lowering copper status. The NOAEL was found to be 0.83 mg Zn/kg bw/day (Scientific Committee on Food SCF), 2003). EFSA has subsequently confirmed this NOAEL of 0.83 mg Zn/kg bw/day established by the SCF in two opinions from 2006 (EFSA, 2006) and 2014 (EFSA, 2014). In addition, the Scientific Committee on Consumer Safety (SCCS) in the opinion on water-soluble zinc salts used in oral hygiene products used in oral hygiene products has used the same endpoints as the EFSA report from 2014 for their safety evaluation (SCCS, 2017).

Derivation of DNELs

RAC supports the approach of the Dossier Submitter to adopt a NOAEL of 50 mg/day or 0.83 mg zinc/kg bw/day. This is based on the absence in humans of any adverse effects for a wide range of relevant indicators of copper-status as critical endpoint as indicated in the EFSA reports (EFSA, 2006, 2014) and supported by the SCCS opinion from 2017 (SCCS, 2017). The lowered iron and copper status was assessed through serum ferritin, haematocrit and ESOD (Erythrocyte superoxide dismutase levels) and inclusion of iron with zinc ameliorates the effect on iron but not on copper status (a key 003 study report, human exposure, (Unnamed, 1989). The NOAEL in this study is less than 0.83 mg Zn2+/kg bw/day. The population in the study reflects only healthy volunteers and it was thus suggested to add an AF of 5 in order to cover the young and more vulnerable population.

A DNEL from this study is estimated to be NOAEL/5 = 0.83/5 = 0.166 mg Zn2+/kg bw/day. Total amount of Zn that may be tolerable can be estimated to be: 0.166 mg Zn/kg bw/day x 60 kg bw = 9.96 mg Zn^{2+} ≈ 10 mg Zn^{2+} per day.

5. Substances with restriction on their use in cosmetic products (CPR) – qualitative evaluation

RAC, in order to assure consistency with other EU legislation, supports the Dossier Submitter's proposal that the following groups of substances can best be assessed in a qualitative manner in the context of this restriction as no further assessment is necessary because such was performed under the CPR, and paragraph 0.5 of Annex I of REACH applies:

- substances on Annex II of CPR (list of substances prohibited in cosmetic products).
- substances on Annex IV of CPR that are not allowed to be used in contact with mucous membranes, eyes or in prolonged contact with the skin (column "g") or subject to other conditions specified in columns "h" to "i" of the Annex (e.g., purity requirements).

The Dossier Submitter assumes that the intrinsic properties will manifest themselves to a higher degree when injected into the dermis in a tattoo than if applied on the body via cosmetic products. RAC agrees with this assumption as a part of a precautionary approach,

while pointing out uncertainties already stated in the section *B.1.1. Description of and justification for targeting of the information on hazard(s) and exposure/emissions)*.

RAC also notes that by this approach hazardous substances (e.g. skin sensitisers) without harmonised classification but included in Annex II or Annex IV of CPR will be in the scope of the restriction.

Appendix 3: Derivation of concentration limits

This Annex supplements Section 1.2.3 (risk characterisation) of the opinion document with further details supporting the RAC conclusions on concentration limits.

Qualitative approach

1. **Substances with predominantly non-threshold health hazards evaluated qualitatively**

For this group of substances it is difficult to identify a reliable dose-descriptor, therefore the health risk was evaluated in a qualitative manner (carcinogens, mutagens, lead compounds, skin sensitisers, skin and eye irritating or corrosive substances).

RAC agrees that when no reliable dose descriptor can be set for a given endpoint[98], a qualitative approach to risk assessment should be chosen as recommended in ECHA guidance Part E (ECHA, 2016) and R.8 (ECHA, 2012), with a few exceptions for substances for which a (semi-)quantitative approach was applied. The purpose of this qualitative risk characterisation is to assess the likelihood that these effects are avoided when receiving a tattoo as indicated in REACH Annex 1, Section 6.5.: "*For those human effects and those environmental spheres for which it was not possible to determine a DNEL or a PNEC, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out*."

The exposure assessment indicates that significant exposure can occur due to the delivery of tattoo inks into the dermis and since these are non-threshold substances it cannot be excluded that risks to consumers can occur.

It is agreed that there is no single, standardised methodology for performing a qualitative assessment. However, traditional operational conditions (OC) and risk management measures (RMM), such as a level of containment and use of personal protective equipment, do not have relevance to the intradermal injection of tattoo inks. This makes the hazard bands presented in ECHA Practical Guide 15 (ECHA, 2016b) and ECHA guidance Part E (ECHA, 2016) depending on the EU hazard classification unsuitable to apply as such. The only way to manage the risk in the case of receiving tattoos is to limit the presence of unwanted substances in tattoo inks.

This use of a qualitative approach is consistent with the approach taken in REACH Annex XVII entries 28, 29 and 30 (restriction of substances classified as CMRs category 1A and 1B to the general public, CL/SCL apply).

Therefore, RAC agrees with the Dossier Submitter proposal that the substances should be restricted in tattoo inks based on the risk from exposure to substances classified with regard to skin irritation/corrosion, eye damage/ irritation, sensitisation, mutagenicity and carcinogenicity and with consideration to the exposure as described in 1.2.5 and Annex B.9, even if a quantitative risk assessment could not be performed. A total ban is not realistic, as this would prevent tattooing as such, so the risk should be managed by setting concentration limits for the chemical substances in tattoo ink, as proposed in the chapter on risk

[98] carcinogens, mutagens, lead compounds, skin sensitisers, skin and eye irritating or corrosive substances

management options (see 2.2).

Carcinogenic or mutagenic substances

For the carcinogenic and mutagenic substances listed in Table A the conditions for restriction are identical in RO1 and RO2. The difference between RO1 and RO2 is only limited in approach to CM substances not listed in Table A that may occur in tattoo inks.

Under RO1, the Dossier Submitter proposed that tattoo inks should not contain carcinogenic or mutagenic substances in category 1A/B or 2. For RO2, the Dossier Submitter proposed that the generic concentration limits (GCL) as well as the specific concentration limits (SCL) under CLP will be applied.

RAC agreed that substances with CMR should not be present in tattoo inks. For the purpose of ensuring the practicality and monitorability of the proposed restriction, sufficiently low CLs are to be derived for these substance groups. Not allowing any presence of carcinogenic or mutagenic substances, category 1A, 1B or 2 in practice means that concentrations of such substances in tattoo inks should be below the available analytical methods for their detection and measurements. However, as stated in section B.1.2.1.3 of the opinion, for the purpose of uniform implementation and enforcement of this restriction in the European Economic Area, a practical concentration limit is proposed in RO2 equal to the GCL or SCL of the carcinogenic and mutagenic substance. However, as the GCL and SCL in the CLP are intended primarily to be used for communication on health hazard of the mixtures, and not for risk assessment, RAC does not recommend their use as concentration limits for CM substances in tattoo inks. Noting Forum's advice, RAC is proposing the setting of a practical concentration limit for all carcinogenic and mutagenic substances in tattoo ink. Since the structures of at least some these CMs resemble those of PAAs and PAHs, the practical concentration limit of 0.00005% w/w (as for PAHs as a group) is proposed for all CM substances (category 1A/B or 2). PAHs are very well studied and potent C/Ms and therefore setting a generic CL for CM substances for this restriction based on them are appropriate

For the **polyaromatic hydrocarbons** (PAHs) with harmonised classification as carcinogenic or mutagenic, the Dossier Submitter proposes both for RO1 and RO2 the same concentration limit as for the eight PAH substances in REACH Annex XVII, entry #50 (6), for toys and childcare articles, namely **0.00005% w/w (0.5 ppm)**, for each individual PAH.

RAC agrees with this proposal, but considers that for benzo(a)pyrene (BaP) a lower concentration limit of 0.0000005%, i.e. **5 ppb**, as set for BaP in CoE ResAP(2008)1, is more appropriate due to its higher carcinogenic potential compared to other PAHs[99]. Namely, in REACH Annex XVII, entry #50 (6) topical exposure to PAHs (including BaP) is assumed ("rubber or plastic components that come into direct as well as prolonged or short-term repetitive contact with the human skin or the oral cavity"), while lower concentration limit (5 ppb) for BaP is in line with national legislation in the Member States which incorporated CoE ResAP. The lower limit for BaP was supported in the Public Consultation (comment #1913),

[99] According to BfR Opinion No 051/2009, 14 October 2009, Polycyclic aromatic hydrocarbons (PAHs) in toys, some dibenzopyrenes (dibenz[a,l]pyrene, dibenz[a,h]pyrene and dibenz[a,i]pyrene) have even greater carcinogenic potency than BaP, but they are not (yet) classified according to the CLP.

which compared concentration limit for all PAHs proposed by the Dossier Submitter with concentration limit for BaP recommended by the CoE ResAP(2008)1.

Skin sensitisation

Although reliable conclusions on prevalence of reactions of sensitisation and ingredients of tattoo inks causally related to sensitisation cannot be drawn due to methodological limitations of epidemiological studies and case reports[100], observations in human population demonstrate that contact allergic dermatitis could be induced by tattoo inks.

RAC considers that available human data, as well as intrinsic property of skin sensitising substances, indicate risk which justifies restriction of these substances in tattoo inks.

The Dossier Submitter, following qualitative approach, proposed two ways of setting concentration limits for skin sensitising substances in tattoo inks:

1) under RO1 a practical concentrating limit of 0.1% w/w to discourage intentional use;
2) under RO2 the generic concentrations limits (GCL; 1.0% for Cat 1, 0.1% for Cat 1A, 1.0% for Cat 1B) and specific concentrations limits as specified under CLP Regulation (substance specific, and lower than the GCLs).

However, RAC is concerned that neither of proposed concentration limits is sufficiently protective for skin sensitisation. Epidemiological data indicate that concentration limits in Part 3 of Annex I of Regulation (EC) No12772/2008 do not necessarily exclude the risk of hypersensitivity reactions, regarding both induction and elicitation (Fischer et al., 2011). In a review study evaluating dose-responses in patch test with several human allergens (metals, preservatives, fragrances), Fischer et al. (2011) concluded that there is "a rather small variation in the elicitation doses between the allergens, for the most sensitive part of the allergic population". Allergen with a median response among evaluated 16 substances (hydroxyisohexyl 3-cyclohexene carboxaldehyde, listed in CPR Annex II), had ED_{10} of around 0.01%, and ED_5 of approximately 0.001% (Johansen et al., 2003). For allergen with ED_{10} at lower 10th percentile (isoeugenol, listed in CPR Annex III, with no harmonised classification), the threshold patch test concentration among the positive patients ranged from 0.0005% to 2% (Andersen et al., 2001). Although these substances have not yet been found in tattoo inks, and isoeugenol is already restricted as being on CPR Annex II list, they are recognised as a part of group of substances representing strong human sensitisers, and could be, potentially used for extrapolation to other substances of similar skin sensitising potency in humans.

RAC, therefore, proposes practical concentration limit of 0.001%, indicated as a level at which at least 5% of already sensitised persons could react to a strong sensitiser.

[100] For example, allergy testing (patch test) was often not performed so exact diagnose could not be established; often unknown composition of applied tattoo ink; false negative result of patch test if the test is not performed with the right substance due to the lack of ingredient information on tattoo inks, due to formation of the allergen (hapten-protein link) inside the skin over a longer period of time, or due to inadequate penetration of tested substance into the skin), as well as difference in pathophysiological response to topical and intradermal application of allergen (immune response other than contact allergy).

RAC proposes this conservative approach pointing out that among evaluated hazards and health effects observed after tattooing, local skin reactions, including those of allergic aetiology are the most prevalent and most consistently related to tattooing. Approximately 1/3 of all adverse tattoo reactions reported by patients at the "Tattoo Clinic" at the Department of Dermatology at Bispebjerg University Hospital, Copenhagen, were considered to be allergic according to clinical criteria set by Serup, et al. (2015b), and that lower doses are needed to induce immunological reaction after intradermal introduction of allergen compared to topical application.

While proposing practical concentration limit, RAC points out that, at least at the present moment, concentration limit at which there is no risk for induction or elicitation of allergic skin reaction is not known. In addition, there is an uncertainty (already discussed in the section B.1.2.1.3) that intradermally applied chemicals can induce stronger (or even pathophysiologically different) immunologic response compared to topically applied chemical at the same concentration. Presently there are no human or animal data which could allow quantification of this difference. Also, it is possible that some substances, which normally would not penetrate the skin due to substance properties (size or physio-chemical properties) and are, therefore, unreactive if applied topically, can cause reactions when injected directly into dermis (DEPA, 2017a).

Skin and eye irritation/corrosion

By qualitative approach, the Dossier Submitter proposed two ways of setting concentration limits for these substances in tattoo inks:

1) under RO1 a practical concentration limit of 0.1% w/w to discourage intentional use;
2) under RO2 the concentration limit for classification in a mixture as specified under CLP Regulation[101].

RAC, however, considers that these limits are not necessarily protective enough, and the same concern has been expressed during the Public Consultation (comment #1898).

For example, at 0.5% of sodium hydroxide (NaOH), which is a SCL for NaOH according to CLP, 61% of tested human subjects (20 out of 33 volunteers) had irritant reaction after 1-hour patch test, and 20% of subjects (6 out of 30) had irritant reaction after 4-hour patch test with 10% of hydrochloric acid, which is a SCL for this substance according to CLP

[101] In CLP, the GCL for substances classified as Cat. 1: Irreversible effects on the eye (Eye Dam. 1) or Skin corr 1A/B/C is ≥ 3% in a mixture classified as Irrev Eye Effects 1 and ≥ 1% but <3% in mixtures classified as Cat. 2: Irritating to eyes (Eye Irrit. 2). The GCL for substances classified as Eye Effects 2 is ≥ 10% in a mixture classified as Rev Eye Effects 2.

The GCL for substances classified as Skin Corr 1A/B/C is ≥5% in a mixture classified as Skin Corr 1 and ≥ 1% but < 5% in mixtures classified as Skin Irr 2. The GCL for substances classified as Skin Irr 2 is ≥ 10% in a mixture classified as Skin Irr 2.

In addition to this, rules of addition apply.

(Basketter et al., 1997)[102]. Occlusive 24 h testing with 5% nonanoic acid induced weak to moderate irritative reaction in 5 out of 12 tested healthy volunteers (Fullerton et al., 2002), although, according to CLP, GCL for this substance (as Category 2 skin and eye irritant) is 10% w/w. It is pointed out that mentioned substances were applied topically, so that even more intense reaction could be expected after intradermal application.

Data for intradermal application of irritants in human population is very limited, except for medical drugs, which are often tested intradermally for diagnostic purposes (evaluation of drug hypersensitivity reactions). Comparing non-irritative concentrations of different classes of drugs applied in patch test and intradermally, intradermal non-irritant concentrations were mainly one order of magnitude (e.g. for local anaesthetics, antibiotics, iodinated contrast media, chemotherapeutics – excluding platinum, glucocorticoids, fluorescein) to two orders of magnitude (for nonsteroidal anti-inflammatory drugs, heparins) lower that those applied in patch testing (Brockow et al., 2013)[103]. Applicability of these data to the restriction proposal is, however, limited. Studies were rarely performed in healthy, non-allergic subjects, different vehicles were used for intradermal and patch tests (or vehicle was not stated), content of other drug's components (e.g. irritants, such as sodium lauryl sulphate, or pharmacologically active substances, capable of enhancing or attenuating irritative response) probably varied between analysed studies (Brockow et al., 2013; Barbaud et al., 2001).

In addition to pharmaceuticals, RAC identified one human study with intradermally applied non-drug skin irritant, sodium lauryl sulphate (SLS), which is a well-known, strong skin irritant in humans[104] (Fairweather et al., 2004). Intradermal application (via microdialysis fibres, during 20 minutes) with 0.1% and 0.5% concentrations of SLS in 12 human volunteers induced dose-related inflammatory reactions (significant difference in skin reddening, increased blood flow and prostaglandin E2 concentration, compared to saline control and 0.01% SLS in the same subject). The effects subsided 40 minutes after application, but it should be noted that after 20-minute exposure period the injection site was perfused for 40 minutes with saline. At 0.01% SLS statistically significant difference in analysed outcomes compared to control was not observed. This value is approximately 100 times lower than the value of 1% SLS recommended by the USA Cosmetic Ingredient Review as a maximal concentration of SLS in products intended for prolonged contact with skin (CIR 1983; CIR 2005).

Animal experiment with 15 known skin irritants comprising different groups of chemicals (acids, alkalis, oxidising substances or those reactive to proteins) showed similar results (Sekizawa et al., 1994). Concentration levels which induced moderate to severe (erosion and necrosis) skin reactions were lower for intradermal than for topical exposure, with factors

[102] As positive reaction was considered any reaction from weakly positive (mild erythema or dryness across most of the treatment site) to strongly positive (strong, often spreading erythema with oedema).

[103] Intradermal *vs.* topical minimal irritative concentration ratio ranged from 2.5 (for some antibiotics and proton pump inhibitors) to 5000 (for chlorhexidine digluconate). Vast majority of ratios was one or two orders of magnitude, however.

[104] SLS does not have harmonised classification. Nevertheless, its irritant properties are well known and it is used in clinical practice and epidemiological research as a standard contact irritant (Fairweather et al., 2004; Kligman and Wooding, 1967).

ranging from 2.5-4 (phosphoric acid, formic acid, dioxane) to 500 (ammonia). For the rest of tested substances, however, the factors were one to two orders of magnitude lower for intradermal application compared to 24-hour topical application, both in rats and mice.

Uncertainty of the comparison between irritant potency of topical and intradermal exposure route is primarily related to potentially different mechanisms involved in irritant response for these two exposure routes, since with intradermal application there is no epidermal barrier. Another uncertainty relates to differences in exposure duration, i.e. single intradermal injection *vs.* 4 or 24 hours topical exposure.

Based on the comparison between irritant potency of topical and intradermal exposure route in which minimal concentrations able to induce irritant response were one to two orders of magnitude lower after intradermal compared to topical application, taking into account an observation that irritative reactions in humans were observed at or even below the concentration levels set in Annex VI to the CLP, and the wide inter-individual variability of sensitivity to irritative reaction caused by chemicals (e.g. two orders of magnitude for SLS; Basketter et al., 1997), RAC proposes a concentration limit for skin/eye irritants and corrosives achieved by **dividing by a factor of 100** the **GCL of 1%** for **Category 2 for skin corrosive substances or eye damage substances**, deriving a value of **0.01%**.

This value is:

- in the range of lowest SCLs set for irritant effects (Cat. 2) in Annex VI to the CLP, i.e. 0.01-0.06% (dibutyltin dichloride and reaction mass of: bis[(2-ethyl-1-oxohexyl)oxy]dioctyl stannane; bis[((2-ethyl-1-oxohexyl)oxy)dioctylstannyl]oxide; bis(1-phenyl-1,3-decanedionyl)dioctyl stannane; ((2-ethyl-1-oxohexyl)oxy)-(1-phenyl-1,3-decanedionyl)dioctyl stannane). GCL and SCLs for corrosive effects (Cat. 1 for skin corrosion and eye damage), as well as GCL and SCLs for irritative effects of Cat. 2 skin/eye irritants, are above this range.
- 10 to 100 times lower than concentration limit set in Annex V to the CPR (list of allowed preservatives, with the conditions) for irritant preservatives found in tattoo inks.

It is considered that biochemical mechanisms responsible for irritative and corrosive response to chemicals differ only to a certain degree, primarily regarding the effects on structure and function of the *stratum corneum*, while some mechanisms, such as inflammatory and/or cytotoxic response in epidermis and dermis, are shared both by irritants and corrosives (ECHA Guidance 2017, Appendix R.7.2–1). Therefore, the severity of adverse responses may determine whether irritation or corrosion occurs (ECHA Guidance 2017, Appendix R.7.2–1). Since RAC considers that not only corrosive, but also irritative effects of injected tattoo inks should be prevented (please see the reasoning stated in the section on Hazards), and that the irritative effects are expected to be observed below corrosive concentrations of the same substance, proposed CL is primarily based on irritative effects, which is expected to be also protective from corrosive effects.

It should be noted, however, that concentration limit proposed by RAC is maybe not protective enough against irritant effects of strong acids and alkalis (e.g. hydrofluoric acid and its salts, sodium and potassium hydroxide, calcium hypochlorite), which SCLs for skin or eye irritancy (Cat. 2) are in the range of 0.1% to 0.5%. Also, RAC points out that while this is a practical

concentration limit to facilitate enforcement, these substances should not be used in tattoo inks.

2. **Substances with non-threshold health hazards evaluated qualitatively and concentration limits set quantitatively (DMELs)**

To determine if there is a risk from tattoo ink constituents and impurities, and in order to derive proposals for limit values of the hazardous constituents to control risk, derived DN(M)ELs for the general population were compared to the exposure from receiving a tattoo, based on following premises:

- The DN(M)EL expressed as mg/kg bw/day
- Body weight of 60 kg
- Tattoo size of 300 cm^2
- Amount of ink[105] injected to a person for a single 300 cm^2 full-colour tattoo:

  300 cm^2 x 14.36 mg ink/cm^2 = 4 308 mg (see previous section)
- Amount of ink injected per kg bw (60kg/person): 72 mg/kg bw/day
- Amount of the substance per kg bw:

  72 mg/kg bw/day x $C_{substance\ in\ the\ ink}$

This value reflecting exposure of the person divided by DN(M)EL results in RCR:

$$RCR = \frac{exposure}{\text{DN(M)EL}} = \frac{72\ \frac{mg\ ink}{kg\ bw\ x\ d}}{\text{DN(M)EL}} \text{ x } C_{substance} < 1$$

Therefore, when a DN(M)EL for an assessed substance is divided by this value, concentration limit ($C_{substance}$) for that substance is derived.

$$Concentration\ limit\ of\ the\ \text{substance in the ink} = \frac{DN(M)EL\ substance\ \frac{mg}{kg\ bw\ x\ d}}{72\ \frac{mg\ ink}{kg\ bw\ x\ d}}$$

The Dossier Submitter's assumptions for calculation are that uptake of pigments is 100%, that impurities released from pigments are completely excreted before next tattooing session, and that the continuous release of impurities does not exceed the concentration in the ink supplied to the body in the initial ink.

(Daily dose of an assessed substance contained in tattoo ink received in one tattooing session could be also calculated by:

fraction of assessed substance in ink * 4 308 mg / 60 kg bw

This value divided by DN(M)EL results in RCR, while when a DN(M)EL for an assessed

[105] It should be noted that 4 308 mg ink applies to total mass of ink product, which contains both colourants and auxiliary ingredients.

substance is divided by this value, concentration limit for that substance is derived.)

Azo colourants and primary aromatic amines (PAAs)

Risk based concentration limit for selected PAAs (listed in Table A of the Background Document)

The Dossier Submitter calculated **risk based limit value** for the concentration of selected PAAs in tattoo ink (Table A in the Background Document) by applying grouping approach in which DMEL value of 2 x 10^{-5} mg /kg bw per day (derived for aniline) was chosen. PAAs are rather quickly eliminated from the body (over a period of a few days or weeks; CHDP, 2015), and accumulation between two tattooing sessions is not expected.

Multiplying the chosen DMEL value with 60 kg body weight, and dividing it by 4 308 mg ink applied in one tattooing session, a limit of 0.28 ppm for each individual PAA was calculated. This figure was rounded to **0.3 ppm (0.00003% w/w)**, applicable for both RO1 and RO2.

Taking into account uncertainties (described in section B.1.2.1.3), RAC agrees with the proposed calculation of risk based limit value for selected PAAs, but considers that it is more appropriate to base DMEL of 4 x 10^{-5} mg /kg bw per day on risk assessment for o-anisidine. This value is supported by DMEL for aniline with corrected assessment factor for inter-species differences, with DMEL for aniline supporting this value. Concentration limit calculated with this DMEL is 0.56 ppm, rounded to **0.6 ppm (0.00006%)**.

Seemingly stricter option would be setting LoD as a concertation limit for all carcinogenic/mutagenic/skin sensitising PAAs (as proposed for carcinogenic/mutagenic substances in RO1). Nevertheless, it has to be taken into consideration that for presently available analytical methods LoDs for PAAs range from 0.5 - 10 ppm (Table 43 in the Background Document).

Taking into account the LoD, technically achievable concentrations and availability of alternatives, **higher concentration limit of 5 ppm (0.0005% w/w)** for each individual PAA has been proposed by the Dossier Submitter.[106] This value represents a concentration level which is met by 75% of the tattoo inks present on the EU market, and is, therefore, considered as technically achievable level. This is in line with the condition for relevant PAAs in tattoo inks set in CoE ResAP(2008)1: "they do not contain or release the aromatic amines listed in Table 1 of this appendix in concentrations that are technically avoidable according to good manufacturing procedures", which allows for unintentional presence of PAAs of concern. RAC notes that although this concentration limit implies a risk level of 1.7*10^{-5}, it is still lower than the lowest SCL set for carcinogenicity, mutagenicity or skin sensitisation in the CLP Annex VI, and supports this higher concentration limit for practical reasons.

Azo colourants

[106] PAAs are also subject to restriction in textiles and leather article in Annex XVII, entry #43 of REACH. All PAA listed on Appendix 8 of entry 43 are included in the scope of the proposed tattoo inks with a concentration limit of 30 ppm, i.e., less strict than the RAC proposed concertation limit in tattoo inks.

For azo colourants a practical approach is chosen. Since a minimal concentration of azo colourants of 5-10% in tattoo ink is normally required to colour the skin, for both RO1 and RO2, a **practical limit of 0.1%** is proposed by the Dossier Submitter, in order to prevent the use of the azo colourants that are in the scope of the restriction.[107]

RAC supports this proposal, since this limit is low enough that could be realistically expected to prevent intentional of addition of azo colourant to a tattoo ink. Also, RAC considers that deriving a DMEL for carcinogenic hazard of azo colourants is not feasible, since an important concern is not only carcinogenicity of a parent colourant, but also the potential for their decomposition to carcinogenic/mutagenic/skin sensitising PAAs. However, the probability and rate of this process is unknown at the present moment.

Substances considered to be impurities in tattoo inks and PMU listed in Table 3 of the CoE ResAP(2008) - semi-quantitative assessment

Lead

RAC upholds a previous opinions based on EFSA's opinion to consider as the maximum exposure to lead a value of 0.05 µg Pb/kg bw/d, which implies that a 60 kg person should maximally be injected with less than 3 µg Pb/day (60 kg x 0.05 µg Pb/kg/day) for the risk characterisation ratio (RCR) not to exceed 1.

For the single session of tattooing a 4 308 mg of tattoo ink is injected and maximum concentration of lead in injected ink should not exceed a value calculated with this formula derived above:

$$Conc.limit\ Pb\ \text{in ink} = \frac{0.00005\ \frac{mg}{kg\ bw\ x\ d}}{72\ \frac{mg\ ink}{kg\ bw\ x\ d}} = 0.00000069\ \text{mg Pb/mg ink} \approx 0.7\ \text{mg Pb/kg}_{ink} = 0.7\ \text{ppm}$$

This **concentration limit for lead** in tattoo ink (**0.7 ppm**) is almost 3 times lower than the maximum allowable concentration for this element in the CoE ResAP(2008)1 (2 ppm). While this limit is reflected in the legislation of those member states that have national legislation based on ResAP(2008), it is not necessarily reflected in the legislation of member states that have instead based their legislation on the previous resolution ResAP (2003), which does not include this limit[37]. Furthermore, other member states do not have legislation based on either of these resolutions.

Based on a report by the JRC (JRC, 2015b), lead has been detected in tattoo inks in the range 0.015-401.5 mg/kg (ppm). Using upper limit of this range, as a realistic worst case, the estimated Pb dose/person administered through injection of tattoo inks at this concentration

[107] Azo colourants are also subject to a restriction in textiles and leather article in Annex XVII, entry #43 of REACH, with concentration limit of 0.1% w/w in mixtures intended for colouring textile and leather articles. The 0.1% w/w was also considered sufficient to discourage the intentional use of azo colourants in tattoo inks (they are not expected to be found as impurities such as PAAs for example) because a minimum concentration of azo colourants of 5-10% in the tattoo ink is normally required in order to be able to colour the skin.

is calculated below.

Table 15. Derivation of concetration limit for lead

Parameter	**Values measured in tattoo ink**	**Value proposed as maximum allowable concentration**
Concentration of Pb present in tattoo inks (mg/kg) (ppm)	0.015 – 401.5	0.7
Maximum Pb concentration in ink (mg/kg) (ppm)	401.5	0.7
Maximum Pb concentration in ink (µg/mg)	0.4015	0.0007
Pb present in 4 308 mg ink used per session at this max. conc. (µg) (based on 4 308 mg ink per session)	≈1730	3.0
Estimated daily Pb dose for a 60 kg person (µg Pb/d)	≈1730	3.0

The risk characterisation ratio is calculated with the following formula

$$(\text{RCR}) = \frac{\text{maximum injected dose } (1730\ \mu\text{g Pb/d})}{\text{maximum allowable dose of } 3\ \mu\text{g Pb/d}} = 576.6$$

The high value of RCR demonstrates that for Pb measured in tattoo ink, the risk is not controlled, which supports lead restriction in tattoo inks.

Arsenic

Using the calculation described at the beginning of this subsection, the Dossier Submitter calculated that the estimated daily internal dose of arsenic following one tattooing session with an ink in which arsenic is present at the maximum permitted level according to ResAP(2008)1 (2 mg/kg), would be:

2×10^{-6} (max. permitted As concentration in ink, expressed as fraction[108]) * 4 308 mg ink/ 60 kg bw = 0.0001436 mg As/kg bw (or 0.144 µg As/kg bw)

Since arsenic has been detected in tattoo inks up to 60 mg/kg (JRC, 2015b), the estimated daily internal dose of arsenic following one tattooing session with an ink in which arsenic is present at a level of 60 mg/kg (as a realistic worst case), is calculated to be:

6×10^{-5} (maximum As concentration detected in ink, expressed as fraction[109]) * 4 308 mg ink / 60 kg bw = 0.0043 mg As/kg bw (or 4.3 µg As/kg bw)

Since the leading health effect is a non-threshold effect (non-threshold carcinogenicity), the Dossier Submitter performed risk characterisation by comparing predicted exposure to a DMEL of 10^{-6}, as an indicative tolerable lifetime cancer risk level for the general population (1 case per 1 000 000 exposed individuals), according to ECHA (2016d).

Taking into account that according to RAC-derived dose-response curve, the excess lifetime

[108] 2 mg/kg = 2 mg/1 000 000 mg = 0.000002 ppm = 2×10^{-6}ppm

[109] 60 mg/kg = 60 mg/1 000 000 mg = 0.00006 ppm = 6×10^{-5} ppm

lung cancer mortality risk is 1.7 x 10^{-3} per µg As/kg bw/day (for oral route), and the excess lifetime lung cancer mortality risk due to arsenic exposure via tattooing could be estimated to:

$$1.7 \times 10^{-3} \times 0.1436 \text{ µg As/kg bw} = 2.44 \times 10^{-4}$$

in the case of arsenic concentration in tattoo ink at the maximum permitted level according to ResAP(2008)1 (2 mg/kg), with resulting "RCR" of 244 (2.44 x 10^{-4}/1 x 10^{-6}), while pointing out that this "RCR" is not related to a no-effect level (DNEL), but to an indicative tolerable risk level for the general population (DMEL) of 10^{-6}; and

$$1.7 \times 10^{-3} \times 4.3 \text{ µg As/kg bw} = 7.31 \times 10^{-3}$$

in the case of maximum arsenic concentration detected in ink (60 mg/kg), with resulting "RCR" of >7 300 (7.31 x 10^{-3} / 1 x 10^{-6}).

The Dossier Submitter concluded that the risk is not adequately controlled even at the maximum permitted level according to ResAP(2008)1[110] and proposed new concentration limit, derived by back-calculation from DMEL (indicative tolerable lifetime cancer risk level of 10^{-6}), as explained in the Background Document. Presented in a more simple way, if for the maximum permitted level of arsenic according to ResAP(2008)1 (2 mg/kg) an "RCR" of 244 has been calculated, the Dossier Submitter proposed **individual concentration limit** 244 times lower than 2 mg/kg, i.e. **0.0082 mg/kg** tattoo ink (or **0.00000082%**).

The Dossier Submitter considers that it is feasible to detecting arsenic in tattoo inks at such a low level on the basis of the LoD of analytical methods available today.

RAC agrees with the Dossier Submitter's approach to risk assessment of arsenic, taking into account the already mentioned uncertainties related to both the exposure scenario and the dose-response curve for arsenic carcinogenicity. RAC considers that this approach is conservative, since it is expected to overestimate the risk. Whole body clearance is fairly rapid for arsenic, with half-times of 40 – 60 hours in humans after oral exposure (according to ATSDR Arsenic, 2007), so accumulation in the body is not expected. Possible overestimation due to linear simplification of dose-response curve for arsenic carcinogenicity is described in section *B.1.2.4. Uncertainties in the risk characterisation*.

During the Public Consultation, however, a concern was raised that risk-based CL proposed is not technically achievable for some colourants. For example, an information was provided that in titanium dioxide pigment with low impurity profile (high purity rutile pigment for cosmetics) the lowest concentration of arsenic measured was 0.000013% (comment #1905).

RAC, therefore, proposes a **practical concentration limit for arsenic** (in addition to risk-based) **of 0.00005%**, as for other carcinogenic/mutagenic substances (which CL is based on CL for PAHs). Namely, it could be expected that arsenic, proposed to be a threshold carcinogen since it does not react directly with the DNA (WHO/FAO 2011; Cohen et al. 2016), is not a more potent carcinogen than non-threshold carcinogenic PAHs. RAC notes that proposed CL

[110] The Dossier Submitter applied also the less conservative **dermal** dose-response relationship for the risk characterisation and the risks was still not controlled ("RCR" of 2.4 was calculated).

(0.00005%) is supported by the range of concentration limits of 0.00002% to 0.00003% set for rice for adult EU population (Regulation EU 2015/1006)[111]. This CL would imply that in one tattooing session a person receives approximately 10% of a typical rice portion in adults. For this CL an excess lung cancer mortality risk of approximately 7 x 10^{-5} could be calculated, according to RAC-derived curve.

Since oral absorption of inorganic arsenic from water and food is more than 90% in humans (ATSDR 2016), no correction for oral absorption is required regarding intradermal application route (i.e. if corrected for 95% oral absorption as reported in ATSDR 2016, practical CL would be 0.0000316%).

3. Substances with assumed threshold health hazard

Methanol

Methanol is present in tattoo inks as denaturing agent of ethanol (in up to 5%), and ethanol is reported to be used in high percentages in the formulation of inks (48% of inks in Germany; JRC, 2015b). Therefore, the Dossier Submitter calculated that a maximum concentration of 2.4% of methanol could be reached in the formulation of ink (as the worst case).

Using formula stated above:

0.024 (fraction of methanol in ink) * 4 308 mg (amount of ink injected in one session) / 60 kg bw

it was calculated that a 60 kg person could receive a maximum dose of 1.7 mg/kg bw per one tattooing session. When divided with DNEL for methanol of 8 mg/kg bw/day, an RCR of 0.22 is obtained, which is a value well below 1. As described in the Background Document, information on the quantity of additives in the formulation of inks is limited, and it is expected to vary significantly among formulators. For example, although high percentage of ethanol (in which methanol is used as denaturing agent) was reported for inks in Germany (48%), lower range (10-30%) was reported by Canada (JRC, 2015b). Nevertheless, RAC considers that the Dossier Submitter's approach for methanol assessment is robust enough, since a higher value (48%) was used in the calculation, and, in any case, the concentration of alcohol is limited in tattoo inks in order to avoid skin irritation.

Dividing DNEL for methanol of 8 mg/kg bw/day by a maximum dose of 1.7 mg/kg bw per one tattooing session, a **concentration limit of 11% w/w** was obtained (rounded value of 10.8%), which equals RCR of 1. This value was applied by the Dossier Submitter for both RO1 and RO2.

RAC agrees with described approach and calculated concentration limit.

Substances classified for reproductive toxicity **(Repr. 1A/B)**

The general approach for risk characterisation is based on risk estimate of a group of 34 reprotoxic substances of diverse structures which currently are included in Annex VI and which are not also classified as carcinogen, mutagen or skin sensitiser.

[111] Concentration limits for rice for adults range from 0.00002% to 0.00003% according to Regulation EU 2015/1006.

In the first option proposed by the Dossier Submitter the lowest DNEL identified for warfarin out of DNELs for reprotoxins classified as category 1A/B is assumed to be sufficiently conservative to represent potential risks from all substances which will be classified as Repr. 1 A/B in the future but currently do not have a harmonised classification as reprotoxins (Cat. 1 A/B). To enable an equal regulation for reprotoxic substances classified currently or in future as Repro. 1A/B the Dossier Submitter proposes, as risk management option 1, a quantitative risk assessment approach based on an overall $DNEL_{general\ population}$, reproductive effects which represents the relevant most critical DNEL derived within the group of currently known reprotoxic "only" substances (see section B.5.9).

As the presence of reprotoxic substances in tattoo inks as ingredient or impurity has not been analysed for most of the assessed substances, the actual risk of those cannot be demonstrated. However, concentration limits can be derived for reprotoxic substances as risk regarding reprotoxic effects has to be assumed if the content in tattoo inks leads to an RCR > 1. The respective concentration limit in the ink can be derived using the total amount of tattoo ink injected into the skin in the relevant exposure scenario (see section B.9.) and the overall $DNEL_{general\ population,\ reproductive\ effects}$.

Dossier Submitter derived the $DNEL_{general\ population}$ of 0.001 mg/kg bw/d for a group of reprotoxic substance using warfarin as the most potent substance out a group of 34 reprotoxic substances considered to be potentially present in tattoo ink (see section B 5.11. This DNEL value of 0.001 mg/kg bw/d can be used to calculate the concentration limit for reproductive toxicants in the worst case scenario:

$$Concentration\ limit\ of\ the\ \text{substance in the ink} = \frac{DNEL\ substance\ \frac{mg}{kg\ bw\ x\ d}}{72\ \frac{mg\ ink}{kg\ bw\ x\ d}}$$

$$\text{Concentration limit for warfarin} = \frac{0.001\ \frac{mg\ substance}{kg\ bw\ x\ d}}{72\ \frac{mg\ ink}{kg\ bw\ x\ d}} = 0.0000139 = 13.9\ mg_{subst}/kg_{ink}$$

CL = 13.9 mg_{subst}/kg_{ink} or 13.9 ppm or rounded off to 0.0014%

Since warfarin is a drug and highly toxic biocide, unlikely to occur in tattoo ink, RAC is of the opinion that the most potent reprotoxic substances already occurring in tattoo ink should be used to set DNEL for that group of substances.

Therefore, a surrogate point of departure ($DNEL_{repr}$) for all reproductive "only" substances (derived using the DNEL for dibutyl phthalate (DBP) as a starting point, and applying an additional factor of 10 to this DNEL), is considered for setting of the concentration limit of reproductive toxicants in tattoo inks.

Taking $DNEL_{repr}$ of 0.0007 mg/kg bw/d into account it can be calculated that maximal dose of „reprotoxic only" substances injected during one tattoo session to a 60 kg person should not be higher than (60 kg x 0.0007 mg/kg bw/d) = 0.042 mg/day.

For the single session of tattooing a 4 308 mg of tattoo ink is injected and maximum concentration of „reprotoxic only" substances in injected ink should not exceed a value calculated with this formula:

0.042mg/4308mg = 0.00000975 mg_{subst}/mg^{ink} = 9.75 mg_{subst}/kg_{ink} ≈ 10mg_{subst}/kg_{ink}

=10ppm

RAC agreed that substances with reprotoxic properties should not be present in tattoo inks. For the purpose of ensuring the practicality and monitorability of the proposed restriction, a sufficiently low CLs are to be derived for these substance groups. Therefore taking into account the above calculations the risk is considered to be controlled if the concentration of reproductive toxicants (Cat. 1A/1B) in tattoo ink is lower than:

$$CL = 10\ mg_{subst}/kg_{ink} \text{ or } 10 \text{ ppm or } 0.001\%$$

RO2 is not supported by RAC because GCLs for ingredients classified as Repr. 1 A/B triggering classification of a whole mixture (in this case a tattoo ink) as Category 1 reproductive toxicant is ≥ 0.3% and as Category 2 reproductive toxicant ≥ 3%. However, the Dossier Submitter has demonstrated that the risk may not be controlled for all substances toxic to reproduction in tattoo inks by applying this limit. Based on the exposure scenario described in section B.9., the GCL of 0.3% would result in a "limit" DNEL of 0.216 mg/kg bw/d, which, if exceeded, would lead to an RCR > 1. Thus, for 14 reprotoxic "only" substances with DNELs < 0.216 mg/kg bw/d, including those currently detected in tattoo inks, the risk would not be controlled given the GCL of 0.3% in RO2.

***Substances classified for reproductive toxicity* (Repr. 2)**

RAC is of the opinion that the major difference between substances classified to category Repr. 1 and Repr. 2 is in the quality and weight of evidence indicating hazard, but the potency of reprotoxicity is not taken into account while comparing with CLH classification criteria. Therefore the potency is not taken into account in hazard classification. The generic and specific concentration limits set in Regulation (EC) No 1272/2008 do not reflect the reprotoxic potency of the substance having harmonised classification, since they are intended to be used for communication on health hazard of the mixtures, but not for risk assessment. Therefore RAC does not recommend to use them as admissible concentration limits in tattoo inks as proposed by Dossier Submitter in RO2. Therefore it is proposed to use for substances classified as Repr. 2 the same concentration limit in tattoo inks as for substances classified as Repr.1.

Substances considered to be impurities in tattoo inks listed in Table 3 of the CoE ResAP(2008) – quantitative assessment

Barium

Soluble barium

Taking into account the calculated DNEL of 0.60 mg Ba/kg bw/day proposed by the Dossier Submitter, and the premises described earlier, the concentration limit (CL) could be calculated:

36 mg Ba/day / 4 308 mg ink = 0.0084 = 0.84% w/w (8 400 ppm) soluble/dissolved Ba

The Dossier Submitter therefore proposed a **concentration limit of 0.84% w/w (8 400 ppm) for soluble barium**, but pointed out that most (or even all) analytical methods available at the present moment cannot differentiate between soluble and insoluble barium.

RAC proposes DNEL of 0.04 mg/kg bw/day, taking into account relatively low absorption of

barium chloride in adult rats (7%). RAC-derived concentration limit is, therefore:

2.4 mg Ba/day / 4 308 mg ink = 0.00056 ≈ **0.05% w/w** soluble/dissolved Ba

taking into account uncertainty related to barium toxicokinetics described in the section *B.1.2.4. Uncertainties in the risk characterisation*.

Insoluble barium

As stated in hazard assessment section, RAC, agrees with the Dossier Submitter that, according to toxicological information published to date, sufficient information that would warrant a restriction on barium sulphate in tattoo inks appears presently not available, and agrees with the Dossier Submitter proposal not to restrict $BaSO_4$ in tattoo inks at the present moment.

However, RAC points out the need to investigate further the factors, both substance- and host-related, responsible for non-specific inflammatory and granulomatous reactions to tattoo inks.

Barium in azo colourants

RAC agrees with the Dossier Submitter not to propose a concentration limit for studied barium azo colourants since either toxicity of these colourants has been associated with the parent azo dye and/or the azo cleavage products and not with the barium moiety, or no DNEL could be derived based on barium due to lack of data.

Copper

Based on the derived DNEL of 1.1 mg Cu/day (or 0.019 mg Cu/kg bw/day for a 60 kg person)[112], 100% uptake for the exposure via subdermal injections, and proposed exposure scenario (in which an amount of 4308 mg ink is applied in a single tattooing session), a safe concentration level for copper in the ink is calculated to be:

1.1 mg Cu/day / 4 308 mg ink/day x 100% = **0.025% of soluble Cu** in the ink (250 ppm)

In the data collected by JRC (JRC, 2015b), the concentration of copper was found to be up to 5%, and up to 2% in DEPA (2012) report. These concentrations would lead to RCRs of 200 and 80, respectively. It could be concluded, therefore, that there is a need to restrict the content of copper in tattoo inks.

Zinc

DNEL used for risk characterisation and justified above in section on hazard assessment amounts to 0.166 mg Zn/kg bw/day, that for 60 kg person make a daily dose of **10 mg Zn^{2+} per day.**

The concentration of Zn in tattoo ink based on data from the JRC Report (JRC, 2015b) will be in a worst case scenario 1 690 mg Zn/kg tattoo ink, resulting in 0.17% Zn (1.69 g x 100/1000

[112] This DNEL value is corrected for 50% oral absoprtion of copper in adult humans subjects with normal dietary copper intake (please see the section B.1.2.1.3).

g=0.17%) in a tattoo ink.

While calculating injected dose of Zinc with tattoo ink, it is assumed as for all other substances being restricted, that a total amount of ink applied during a large tattoo (300 cm^2) is 4 308 mg ink per daily session (14.36 mg ink/cm^2 x 300 cm^2).

Thus, during such tattooing the total dose of injected zinc in worst case scenario would be a product of 4 308 mg ink multiply by the concentration of zinc in tattoo ink:

Dose of zinc in worst case scenario = 4 308 mg ink x 0.17/100 = **7.3 mg of Zn^{2+}/person**

The risk to human health posed by Zn^{2+} in tattoos is estimated by the ratio of the exposure to DNEL, which for the controlled risk should not exceed 1 as shown in the equation below:

Risk = Exposure/DNEL >1

RCR= 7.3 mg/10 mg =0.73 which is <1 and thus the risk is controlled

Derivation of specific concentration limit for zinc

Concentration limit for zinc is derived based on a dose for which RCR = 1, then Zn exposure equals to 10 mg zinc in 4 308 mg of ink (0.166 mg/kg bw x 60 kg = 9.96 mg zinc) and that gives an amount of zinc in 100 mg of tattoo ink 10 x 100/4308 = 0.23 mg ≈ 0.2 mg, or 0.20% w/w, or 2 000 ppm.

In conclusion, a concentration limit value of 2 000 ppm or 0.20% for Zn^{2+} in tattoo ink leads to RCR <1.

Conclusion

In conclusion, the RCR for zinc measured in tattoo inks is below one and thus, there is no risk due to the content of zinc in tattoo inks. Thus, it may be concluded that zinc does not have to be restricted in tattoo inks. A recommended limit value would be 0.23% w/w to ensure future concentration of zinc does not exceed 2 300 ppm.

Remaining substances on Table 3 of the CoE ResAP(2008)1

For the remaining substances on Table 3 of the CoE ResAP(2008)1, the Dossier Submitter proposes to carry forward the limits in the CoE ResAP(2008)1 (with an exception of nickel), as there are no more recent assessments that suggest the need for deviation from ResAP limits, and no DN(M)EL have been derived for cadmium, cobalt, chromium (VI), mercury, nickel, selenium, antimony and tin. All these substances, except tin, are also captured in the group assessments related to the relevant harmonised classification.

In the case of **nickel** (Ni) (Ni has harmonised classification as a skin sensitiser Cat.1, STOT RE 1, and carcinogenic substance Cat.2, while nickel oxides are classified as Carc. 1A, STOT RE 1 and Skin Sens. 1), surveillance/monitoring data from three member states (IT, DK, DE) indicate that the majority of the inks in which Ni was measurable contain Ni as impurity in an amount of 5 mg/kg or less. Due to the limited number of samples which were analysed in the monitoring programs, a concentration limit of 0.001 % w/w or less was proposed by the

Dossier Submitter for Ni. This value does not take into account the sensitising properties of Ni for which no threshold in the context of tattooing can be established due to lack of data. In the absence of more extensive data, RAC recommends to reduce the Dossier Submitter's proposal for practical limit concentration of nickel in tattoo inks from 0.001% (10ppm) to 0.0005% (5ppm), pointing out that concentration of strong sensitisers in tattoo inks should be lowered to a minimum.

Regarding other remaining substances on Table 3 of the CoE ResAP(2008)1 that are carcinogenic/mutagenic or listed on Annex II of the CPR, RAC proposes to apply practical concentration limit of 0.00005%, as already proposed for these groups of substances. This applies for cadmium, chromium (VI), mercury, antimony, cobalt and organometallic tin.

Antimony does not have harmonised classification, but its compounds have (e.g., antimony trioxide is classified as Carc. 2, and antimony trichloride as Skin Corr. 1B), and antimony and its compounds are listed in Annex II of the CPR (entry # 40). RAC, therefore, proposes for antimony the same concentration limit as for other substances listed in Annex II of the CPR (i.e., 0.00005%).

Cobalt is presently classified as Resp. Sens. 1 and Skin Sens. 1, but RAC opinion on cobalt (CLH-O-0000001412-86-172/F), proposing its harmonised classification also as Carc. 1B, Muta. 2 and Repr. 1B, is adopted in September 2017. RAC proposes to set concentration limit for cobalt same as for other carcinogenic and mutagenic substances (i.e., 0.00005%).

Concentration limit of 0.00005%, which is from the aspect of protection of human health rather close to that recommended by CoE ResAP(2008)1 (i.e., 0.00002%), is proposed for **cadmium**, **chromium (VI)** and **mercury** for the sake of making the restriction proposal simpler (and, consequently, to promote better compliance.

Regarding **selenium** RAC agrees with the Dossier Submitter's proposal to carry forward the practical concentration limit set in Table 3 of the CoE ResAP(2008)1 (i.e., 0.0002%) until new risk assessment is available for this essential element. Namely, although selenium is listed on Annex II of the CPR and it has harmonised classification for acute oral and inhalation toxicity and repeated toxicity (STOT RE 2), it is not classified as carcinogenic/mutagenic, reprotoxic or skin sensitising chemical.

Tin, on the other hand, is not listed on Annex II of the CPR and it does not have harmonised classification. Its organic salts, however, are classified as carcinogenic/mutagenic, reprotoxic, skin sensitising, skin irritating or corrosive, or eye irritating or damaging. RAC, therefore, proposes concentration limit only for organotin compounds (0.00005% as for carcinogenic/mutagenic substances).

4. Substances with restriction on their use in cosmetic products (CPR) – qualitative evaluation

Under the CPR, substances on Annex II are prohibited in cosmetic products in a way that they are enforced at a limit of detection (LoD). Under RO1 the Dossier Submitter proposes the same approach. As the Dossier Submitter points out, a disadvantage to this approach is that

it is difficult to differentiate between intentional and non-intentional use, which is solved under the CPR by allowing traces of prohibited substances if they are found in cosmetic products (e.g. impurities), but are not intentionally added.

This could be avoided under RO2, which allows small amounts of these substances in tattoo inks, namely less than 0.1% w/w (concentration limit proposed as a practical limit aiming to discourage intentional use).

RAC considers that the first option (RO1) is difficult to enforce (please see the section B.3.1.3), and that the second option (RO2) is not protective enough. Since Annex II comprises an array of hazardous substances among which are those classified for hazards relevant for tattooing, RAC proposes to apply for Annex II substances the lowest CL set for groups of substances with harmonised classification included in the Annex. This in this case is the practical limit set for CMs of 0.00005%. The carcinogenic and mutagenic substances represent the largest group of substances on Annex II: approximately, 47% of all.

The same approach is proposed for colourants listed in Annex IV, column "g".

The Dossier Submitter proposed, both for RO1 and RO2, that the remaining 119 substances (colourants) with conditions on their use in columns "h" and "i" of Annex IV are allowed in tattoo inks if the specified requirements for their use (in these same columns) are met. The requirements include e.g. purity, constituents, concentration limits, or particle size. This is in line with the argument that substances applied into the skin will elicit the same or greater effects in comparison to if applied on the skin.

RAC supports the Dossier Submitter's proposal since at the present moment no data are available to assess the risk following intradermal application of these substances, but points out the need to reconsider these conditions in restriction's review, i.e. as soon as new data needed for re-assessment become available.