

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/[reference code to be added after the adoption of the SEAC opinion]

Adopted

20 November 2018

20 November 2018**ECHA/RAC/RES-O-0000001412-86-240/F****29 November 2018****ECHA/SEAC/[reference code to be added after the adoption of the SEAC opinion]****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 **[date of adoption of the opinion]**. [The deadline for the opinion of SEAC was in accordance with Article 71(3) of the REACH Regulation extended by **[number of days]** by the ECHA decision **[number and date]**]¹.

[The opinion takes into account the comments of interested parties provided in accordance with Article[s 69(6) and]⁵ 71(1) of the REACH Regulation.] [No comments were received from interested parties during the public consultation in accordance with Article[s 69(6) and]³ 71(1)]⁶.

The opinion of SEAC was adopted **by [consensus.][a simple majority]** of all members having the right to vote. [The minority position[s], including their grounds, are made available in a separate document which has been published at the same time as the opinion.]⁶.

¹ Delete the unnecessary part(s)

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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)

<p>a) Substances in Part 3 of Annex VI to Regulation (EC) No 1272/2008 classified as:</p> <ul style="list-style-type: none"> – 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 <p>b) Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009</p> <p>c) Substances on Annex IV of Regulation (EC) 1223/2009 that are subject to conditions in columns g to i of that Annex</p> <p>d) Substances in Table A⁴</p>	<ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> a. Tattoo inks shall not contain the following substances: <ol style="list-style-type: none"> 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) 1223/2009² iii. Substances in Annex IV of Regulation (EC) 1223/2009 with the following conditions in column g of that Annex: <ul style="list-style-type: none"> • 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: <ol style="list-style-type: none"> i. Skin sensitisers, category 1, 1A and 1B ii. Skin corrosive or irritant substances, category 1, 1A, 1B, 1C, and 2³ iii. Serious eye damage/eye irritant, category 1 and 2³ c. Tattoo inks shall not be placed on the market if they contain substances that are toxic to reproduction: <ol style="list-style-type: none"> 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,⁴ 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:
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² This provision is recommended to apply one year after the substance is listed on Annex II

³ The concentration limit applies to each individual substance

⁴ Table A contains methanol, impurities listed in Table 3 of CoE ResAP(2008)1, PAAs, and azo dyes.

	<p>a. paragraph 1.a.ii) and 1.a.iii) does not apply to substances (colourants) listed in Table B⁵ or</p> <p>b. paragraph 1 does not apply to substances that are gases at standard temperature and pressure.⁶</p> <p>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.</p> <p>5. Tattoo inks not meeting the requirements specified in paragraphs 1 to 4 shall not be used in tattoo procedures.</p> <p>6. The person responsible for the placing on the market of a tattoo ink shall ensure that the label provides the following information:</p> <p>a. The intended use of the mixture as a tattoo ink;</p> <p>b. A reference number to uniquely identify the batch;</p> <p>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;</p> <p>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;</p> <p>e. The phrase "Contains nickel. Can cause allergic reactions." if the tattoo ink contains nickel below the concentration limit specified in Table A.</p> <p>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.</p> <p>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.</p> <p>The labelling shall be clearly visible, easily legible and appropriately durable.</p> <p>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.</p> <p>Where necessary because of the size of the package, the labelling information shall be included in the instructions for use.</p> <p>The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure.</p> <p>7. Definitions for the purpose of this restriction entry</p> <p>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 "permanent make-up") is made.</p> <p>b. Tattoo procedure (also referred to as permanent make-up,</p>
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⁵ 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

⁶ 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.

	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.
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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)

<p>a) Substances in Part 3 of Annex VI to Regulation (EC) No 1272/2008 classified as:</p> <ul style="list-style-type: none"> - 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 <p>b) Substances in Table A⁴</p> <p>c) Substances in Table C⁷</p> <p>d) Substances in Table D⁸</p>	<p>1. Tattoo inks shall not be placed on the market if they contain:</p> <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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 2¹⁰ iv. Serious eye damage/eye irritants, category 1 and 2¹⁰ b. skin sensitisers in excess of 0.01% w/w for category 1A and 0.1% for category 1 or 1B. <p>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.</p> <p>2. Tattoo inks shall not be placed on the market if they contain the substances listed in Table A⁴, 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.</p> <p>3. Unless already specified in paragraphs 1 or 2, tattoo inks shall not be placed on the market if they contain the substances in:</p> <ul style="list-style-type: none"> a. Table C⁷ in concentrations exceeding 0.1 % w/w and b. Table D⁸ in concentrations exceeding 0.1 % w/w. <p>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.⁹</p> <p>5. By way of derogation:</p> <ul style="list-style-type: none"> a) paragraph 3 shall not apply to substances (colourants) listed in Table B or
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⁷ Table C contains substances in Regulation (EC) 1223/2009 as of July 2017 prohibited for use in cosmetic products, i.e., Annex II.

⁸ 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).

¹⁰ The concentration limit applies to each individual substance.

<p>e) Substances in Table E⁹</p>	<p>b) paragraph 1 shall not apply to substances that are gases at standard temperature and pressure.¹¹</p> <p>6. Tattoo inks not meeting the requirements specified in paragraphs 1 to 5 shall not be used in tattoo procedures.</p> <p>7. The person responsible for the placing on the market of a tattoo ink shall ensure that the label provides the following information:</p> <ul style="list-style-type: none"> 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. <p>The labelling shall be clearly visible, easily legible and appropriately durable.</p> <p>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.</p> <p>Where necessary because of the size of the package, the labelling information shall be included in the instructions for use.</p> <p>The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure.</p> <p>8. Definitions for the purpose of this restriction entry</p> <ul style="list-style-type: none"> 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. <p>9. The restriction shall apply one year after its entry into force.</p>
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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.

⁹ 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.

¹¹ 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.

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

<p>a) Substances in Part 3 of Annex VI to Regulation (EC) 1272/2008 classified as:</p> <ul style="list-style-type: none"> – 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 – serious eye damage/eye irritation, category 1 or 2 <p>b) Substances prohibited for use in cosmetic products as listed in Annex II of Regulation (EC) 1223/2009</p> <p>c) Substances on Annex IV of Regulation (EC)</p>	<p>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:</p> <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> • Rinse-off products • 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;¹² f. Toxic to reproduction Category 1A, 1B or 2 in concentrations greater than 0.001 % w/w. <p>2. Tattoo inks shall not be placed on the market if they contain</p>
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¹² The concentration limit applies to each individual substance.

<p>1223/2009 that are subject to conditions in columns g to i of that Annex</p> <p>d) Substances in Table A⁴</p>	<p>substances listed in Table A,¹³ exceeding the specified concentration limits.</p> <ol style="list-style-type: none"> 3. By way of derogation paragraph 1 does not apply to substances that are gases at standard temperature and pressure.¹⁴ 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: <ol style="list-style-type: none"> 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. <p>The labelling shall be clearly visible, easily legible and appropriately durable.</p> <p>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.</p> <p>Where necessary because of the size of the package, the labelling information shall be included in the instructions for use.</p> <p>The information on the label shall be made available to any person before undergoing tattooing procedure by the person performing the procedure.</p> 7. Definitions for the purpose of this restriction entry <ol style="list-style-type: none"> 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.
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¹³ Table A contains methanol, PAHs, other impurities listed in Table 3 of CoE ResAP(2008)1, PAAs, and azo dyes.

¹⁴ 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.

	<p>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.</p> <p>8. The restriction shall apply one year after its entry into force.</p>
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Note: [Supplementary Table A to the RAC modified RO1 is in Appendix 1 of this opinion.](#)

A.2. THE OPINION OF SEAC

See SEAC 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:

Tattoo¹⁵ inks are mixtures of colourants¹⁶ 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 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 States¹⁷ 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

¹⁵ 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.

¹⁶ Colourant is the commonly used denomination for pigments, lakes and dyes that are coloured molecules.

¹⁷ Belgium, France, Germany, Netherlands, Spain, Sweden and Slovenia.

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
 - 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 developed¹⁸ 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 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 lifespan¹⁹.
- 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

¹⁸ 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.

¹⁹ 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

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 Legislation²⁰ could add to the risk 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 approach²¹: 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 compounds²². Substances only classified for carcinogenicity or mutagenicity through

²⁰ 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. methyl dibromo 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 products during storage). On the other hand, methyl dibromo 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.

²¹ REACH Annex I para 1.1.2 and ECHA Guidance R.8.

²² For the purposes of deriving a concentration limit for lead a semi-quantitative assessment has been made.

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 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/m³ 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 colourants. 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 2×10^{-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 restriction²³.
 - 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

²³ Any azo colourants classified as C and M or on Annex II of CPR will also be in the scope of the restriction.

identified from available studies and DNELs were derived in accordance with ECHA guidance R.8.²⁴ 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 DNELs_{general population, reproductive effects} for 27 reprotoxic substances 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 4: 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.

²⁴ 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.

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.²⁵ 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. Key elements underpinning the RAC conclusion(s):

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 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:

²⁵ 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.

- **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

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 inks²⁶

Details of the hazard assessments of substance groups and individual substances are given in Appendix 2 of the opinion, while derivation of concentration limits is described in Appendix 3.

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

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.

²⁶ See Appendix 2 to this opinion for more detailed explanations for each of the categories.

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 nature²⁷. 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, 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.²⁸

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

²⁷ 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.

²⁸ 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).

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-ethoxynaphthalene CAS 293733-21-8 and 2,4-xylydine EC 202-440-0 / CAS 95-68-1). RAC proposes to carry forward to the risk characterisation of PAAs a **DMEL value of 4×10^{-5} mg/kg bw per day** for o-anisidine as a proxy for all PAAs.²⁹

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 polycyclic 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

²⁹ DMEL value for aniline of approximately 2×10^{-5} mg/kg bw/day derived by the Dossier Submitter has been corrected by RAC to 4.6×10^{-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 4×10^{-5} mg/kg bw/day for o-anisidine. For detailed justification, please see Appendix 2 of RAC opinion.

authorisation process)³⁰ and on the evaluation of the occupational exposure limits (OELS) for arsenic acid and its inorganic salts, particularly with reference to its carcinogenicity.³¹

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 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/m³ (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, DNELs_{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

³⁰ 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.

³¹ ECHA, 2017. Committee for Risk Assessment (RAC) opinion on arsenic acid and its inorganic salts (29 May 2017), s.l.: European Chemicals Agency.

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 lakes³² (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 (BaSO₄), as this is by far the most widely used insoluble barium salt. BaSO₄ 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).

³² 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).

RAC agrees with the Dossier Submitter's proposal not to restrict BaSO₄ 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)³³ 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 15:3³⁴ and Pigment Green 7 are phthalocyanines and two essential colourants in tattoo inks.

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).

³³ a definition of 'soluble' Cu in the context of tattoo inks is lacking

³⁴ 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).

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 phthalimide³⁵ (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

³⁵ 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).

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:

- 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 5.

Only one exposure scenario has been developed, consisting of isolated single tattoo sessions on 300 cm² 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 5. 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	100%
Bioavailability of pigments - Percentage of pigment removed from tattoo area by body fluids	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 cm²), 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 cm² skin on which 14.36 mg ink/cm² is applied in one session), which is later used in the risk characterisation.³⁶

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

³⁶ See next section for explanation of assumptions.

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 cm² 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 cm² 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 cm² (median of 600 cm²). When this value was corrected for full-colour tattoo (based on tattoo artists' responses, 300 cm² 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 off 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/cm²). 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/cm²)³⁷. This is higher than in other reports (1.2 mg ink/cm² as the highest value found in experimental study of Prior, 2015; 1 mg ink/cm² 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/cm². 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 cm² skin on which 14.36 mg ink/cm² is applied in one session), for use in the risk characterisation.

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).

³⁷ 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).

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) MANAGER 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/ irritant, 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 (BMDL₀₁/10).

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 limits³⁸

The concentration limits supported by RAC are set out in Table 6 (i.e., RAC modified RO1).

Table 6 Concentration limits proposed by the Dossier Submitter and RAC

Substance group	DS Concentration limits (% w/w)		RAC modified RO1 Concentration limits (% w/w)			Reason for deviation from Dossier Submitter's proposal
	RO 1	RO 2	Risk-based proposal	Practical approach	Justification for practical CL	
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 classifications as CM	0.00005	0.00005	Should not contain	0.00005 BaP: 0.0000005% (5 ppb)	as per CL for toys in Annex XVII, entry #50 BaP: as in Table 3 of CoE ResAP(2008)1	Lower CL is proposed for BaP, 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	No deviation from practical CL of 0.0005% proposed by the Dossier Submitter, which is

³⁸ See Appendix 3 to this opinion for further details

Substance group	DS Concentration limits (% w/w)		RAC modified RO1 Concentration limits (% w/w)			Reason for deviation from Dossier Submitter's proposal
	RO 1	RO 2	Risk-based proposal	Practical approach	Justification for practical CL	
					practical reasons for higher limit (technical achievability)	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 1 or 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 R hazards and Annex II of CPR	0.00005	as for substances on Annex II of the CPR	Group approach (as for other Annex II CPR substances) to 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	-

Substance group	DS Concentration limits (% w/w)		RAC modified RO1 Concentration limits (% w/w)			Reason for deviation from Dossier Submitter's proposal
	RO 1	RO 2	Risk-based proposal	Practical approach	Justification for practical CL	
					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) MANAGER 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 papulonodular reactions, since the intradermal route is not tested in regular toxicological studies, or sun-related adverse reactions of tattooed skin³⁹ (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.

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

³⁹ 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).

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 in 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 full quantitative analysis of the risks of all substances that are currently used in tattoo inks is possible, the available measured values for certain hazardous substances indicate that risks for human health cannot be excluded. 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 MS.

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

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.

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 evaluated 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 6 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 powdered 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”⁴⁰ 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 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 $\geq 0.01\%$ 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**⁴¹ 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

⁴⁰ 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.

⁴¹ 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

substance groups and individual substances (see Appendix 2 and 3 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 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-based⁴², for others a practical approach has been proposed⁴³, and for some substances, CLs were transferred from other legislation⁴⁴ or CoE ResAP(2008)1⁴⁵, 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.⁴⁶

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 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.⁴⁷

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

⁴² carcinogens/mutagens under RO1, reproductive toxicants, methanol, arsenic, barium, copper

⁴³ skin sensitisers, skin/eye irritants/corrosives, azo colourants, PAAs

⁴⁴ CPR substances under RO1 and PAHs

⁴⁵ cadmium, antimony, tin, mercury

⁴⁶ See footnote 30

⁴⁷ 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.

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:

- 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;⁴⁸
- 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 6). 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.

⁴⁸ 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."

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 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.⁴⁹ In 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)⁵⁰. 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

⁴⁹ 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).

⁵⁰ 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."

adequate alternatives.

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).⁵¹ 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.⁵²

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.

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

⁵¹ Chronic excessive exposure may produce a toxic syndrome called "bromism", characterized by behavioural changes, hallucinations, psychosis, ataxia, irritability, headache, and confusion etc. (POISINDEX, 2018).

⁵² 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.

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 strengthened 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 arise⁵³.

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.

Justification for the opinion of SEAC

B.3.1.4. Summary of proposal:

Add summary of Dossier Submitter proposal from the Impact Assessment section of the Annex XV restriction report.

B.3.1.5. SEAC conclusion(s):

Add conclusion of SEAC

B.3.1.6. Key elements underpinning the SEAC conclusion(s):

Add analysis that justifies the conclusion given above¹²

⁵³ 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 is 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.

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 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 or 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.⁵⁴ 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

⁵⁴ 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.

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 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/w⁵⁵). 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 CL (0.00007%) in two public consultation comments (#1893, #1931). One

⁵⁵ 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".

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 report⁵⁶ 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 exist. 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 substances as groups of substances with harmonised classification);⁵⁷ 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

⁵⁶ Swedish Medical Products Agency (SMPA) report 2018-04-23: Kontroll av tatueringsfärger för tatuering och permanent makeup

⁵⁷ In effect, this restricts 17 additional substances for which there is information on presence in tattoo inks in comparison to the CoE resolutions.

Appendix 3 (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.

B.3.3.1.2. SEAC conclusion(s):

Add conclusion of SEAC

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

Add analysis that justifies the conclusion given above¹²

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, hyperkeratotic, 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 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):

Add conclusion of SEAC.

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

Add analysis that justifies the conclusion given above¹²

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):

Add conclusion of SEAC.

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

Add analysis that justifies the conclusion given above¹²

B.3.3.4. Overall proportionality

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 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.

B.3.3.4.3. Key elements underpinning the RAC and SEAC conclusion(s):

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.

B.3.3.5. Uncertainties in the proportionality section

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.

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 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.

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

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.⁵⁸

RO2 is expected to be simpler in its content and format⁵⁹ 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.

The Dossier Submitter states that analytical methods exist for all groups of substances in

⁵⁸ 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.“

⁵⁹ 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 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,⁶⁰ analytical methods are expected to be available (with azo colourants as an exception⁶¹), 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

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

⁶⁰ 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.

⁶¹ 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).

proposed restriction will be manageable for Member States' Competent Authorities as well.

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 considers the proposed restriction to be monitorable.

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

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.

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):

Add conclusion of SEAC.

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

Add analysis that justifies the conclusion given above¹²

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Appendix 1: Supplementary Tables A to RAC 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 7: Supplementary Table A to RAC 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-phenyldiamine**	2,4-toluenediamine	202-453-1	95-80-7	0.0005% w/w
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

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
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-phenylenediamine**	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
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

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
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
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	3-hydroxy-4-[(2-methyl-5-nitrophenyl)azo]-N-(o-	229-681-4	6655-84-1	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
(PR17)/CI 12390	tolyl)naphthalene-2-carboxamide			
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
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'-biphenylene)bis(azo)]bis[2',5'-	239-160-3	15110-84-6, 14110-84-	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
	dimethoxyacetoacetanilide]		6	
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
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-disulphonate	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-	223-942-6	4129-84-4	0.1% w/w

Substance name	Other regulatory process names	EC#	CAS#	Proposed concentration limit
	sulphonatobenzyl]amino]phenyl]methylene]cyclohexa-2,5-dien-1-ylidene](ethyl)(3-sulphonatobenzyl)ammonium, sodium salt			
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
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 colourants⁶², 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-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 promotor (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.

⁶² The Dossier Submitter has assumed that the azo colourants decompose and some of the decomposition products are carcinogenic or mutagenic.

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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 limit⁶³ 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 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

⁶³ 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.

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 nature⁶⁴. 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 allergenic 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 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

⁶⁴ 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.

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

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- are listed in Table 1 of CoE ResAP(2008)⁶⁵; 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, and in Annex I, **Error! Reference source not found.** in this opinion (with designation showing according to which criteria they were included in the list).

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 ResAP(2008)¹ (6-amino-2-ethoxynaphthalene CAS 293733-21-8 and 2,4-xylydine 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

⁶⁵ 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

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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 000⁶⁶ to this value, a DMEL of approximately 2×10^{-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 extrapolation⁶⁷. Applying HtLF of 250 000 to HT25, a DMEL of approximately 4×10^{-5} mg/kg bw/day was derived⁶⁸.

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 2×10^{-5} mg/kg bw per day, carried forward in the risk assessment for PAAs.

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

⁶⁶ 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)

⁶⁷ 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.

⁶⁸ 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.

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(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 Guidance⁶⁹, 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 high-to-low dose factor (250 000 for T25 as a PoD) is considered sufficiently conservative to cover for these differences.⁷⁰ Given this, the DMEL for aniline should be corrected. Applying a factor 4 to aniline instead of 10 results in a DMEL of 4.6×10^{-5} mg/kg bw/day, which compares well to the DMEL for o-anisidine (4×10^{-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 4×10^{-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 degradation⁷¹.

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

⁶⁹ ECHA Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, 2012

⁷⁰ 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."

⁷¹ 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).

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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 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

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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 fetuses) 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

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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

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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)⁷² and on the evaluation of the occupational exposure limits (OELS) for arsenic acid and its inorganic salts, particularly with reference to its carcinogenicity.⁷³

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) assessment⁷⁴, and among the models with a good fit to the data, the linear model was chosen for dose-response curve for lung tumours in humans exposed via drinking water:

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

Since in the above mentioned prospective study only total arsenic was measured (without

⁷² 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.

⁷³ ECHA, 2017. Committee for Risk Assessment (RAC) opinion on arsenic acid and its inorganic salts (29 May 2017), s.l.: European Chemicals Agency

⁷⁴ 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".

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/m³ (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/m³) 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/m³ (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

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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, DNELs_{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

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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 embryofetal 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: $2 \text{ mg/kg bw/d} / 300 = 0.00666 \approx \text{DNEL}$ 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

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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 indicates 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.

$$\text{Surrogate DNEL}_{\text{reprs}} = 0.007 \text{ mg/kg/d}/10 = 0.0007 \text{ mg/kg/d}$$

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 known⁷⁵ (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

⁷⁵ 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).

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).

Human⁷⁶ and animal data do not indicate carcinogenicity, genotoxicity, reproductive toxicity, skin sensitisation, or skin or eye irritation potential of barium chloride and barium carbonate.⁷⁷ 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)⁷⁸, with LOAEL of 4000 ppm barium chloride dihydrate, at which kidney lesions (tubular dilatation) were observed, as well as some other toxic effects

⁷⁶ 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.

⁷⁷ 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 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).

⁷⁸ 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).

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(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 (BMDL₀₅ of 61 mg Ba/kg bw/day for a 5% increase in the incidence of nephropathy in male mice)⁷⁹.

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. 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 (BaSO₄), 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). BaSO₄ 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 BaSO₄ is analysed for presence of soluble barium salts, as required for medical or cosmetic products.

Although BaSO₄ 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.

⁷⁹ 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.

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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 BaSO₄. The use of BaSO₄ 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 BaSO₄ 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 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 BaSO₄ 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, carboxymethylcellulose, 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).

BaSO₄, 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 BaSO₄ becomes systemically available after inhalation exposure (Konduru et al., 2014). Namely, after short-term inhalation exposure, BaSO₄ 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 BaSO₄ 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)⁸⁰, which is probably also the case in baritosis (a benign pneumoconiosis in workers exposed to barium sulphate dust). Namely, systemic toxic effects of BaSO₄ were not observed in workers with baritosis, although presence of barium in regional lymph nodes has been detected (Dosios

⁸⁰ 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).

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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 (BaSO₄ is used in bone cement as a radiopaque agent). Low grade lung tissue inflammation was noted after 90-day inhalation exposure to BaSO₄ 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 in alveolar epithelial type II cells was not observed (Schwotzer et al., 2018).

It is well described that BaSO₄, 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 BaSO₄ release rate from bone cement is limited. Based on experimental data with simulation of mechanical wearing process of BaSO₄-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 BaSO₄, systemic effects are unlikely to occur, as demonstrated by *in vivo* experiment in rabbits (Acarturk et al., 2008) and by the fact that BaSO₄ 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 BaSO₄ 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 BaSO₄ from a tattoo pigment will be extensive and fast enough to lead to systemic toxicity similar to that induced by soluble barium salts. BaSO₄ 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 BaSO₄ as radiopacifier in bone cement as well as from recent inhalation studies, indicate that BaSO₄ particles are capable of inducing local inflammatory response in exposed tissues. Question remains whether phagocytosed BaSO₄ 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 BaSO₄ 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 BaSO₄ in fat pads of guinea pigs (Goldner and Adams, 1977). However, no data on BaSO₄ 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

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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 BaSO₄ that would trigger its restriction in tattoo inks, RAC agrees with the Dossier Submitter's proposal not to restrict BaSO₄ 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 8 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 ⁸¹ , 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 for use preparation 3%)	Observed adverse effects (hemolysis, splenomegaly, hemosiderosis, bone marrow hyperplasia, increased urine bilirubin) in toxicological studies seem unrelated to the contribution of Ba ²⁺ ion ⁸² , and are likely due to the 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-	Not included in CPR Annex IV (thus not allowed in cosmetic	No DNEL could be derived due to lack of data (no toxicological information was identified for this pigment)

⁸¹ Since similar effects were not observed in NTP studies with barium chloride (NTP, 1994) at Ba²⁺ ion doses 10-20x higher in rats and mice, respectively.

⁸² Since the effects were observed in animal studies with sodium salt of the pigment, which did not include exposure to Ba²⁺ ion.

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disulphonato-1-naphthyl)azo]benzoate	products)	
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

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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) database⁸³, 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).

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

⁸³ 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.

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(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 contraception⁸⁴ (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 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),

⁸⁴ The copper used in copper-containing IUDs is quite pure, with very low content of nickel (Fage et al., 2014).

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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-

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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 LD₅₀ 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 (ZnCl₂) 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, ZnSO₄

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(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 Zn²⁺ ≈ 10 mg Zn²⁺ 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).

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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.

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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 endpoint⁸⁵, 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 management options (see 2.2).

Carcinogenic or mutagenic substances

For the carcinogenic and mutagenic substances listed in Table A the conditions for restriction

⁸⁵ carcinogens, mutagens, lead compounds, skin sensitisers, skin and eye irritating or corrosive substances

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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 PAHs⁸⁶. 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), 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

⁸⁶ 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.

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of epidemiological studies and case reports⁸⁷, 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 ED₁₀ of around 0.01%, and ED₅ of approximately 0.001% (Johansen et al., 2003). For allergen with ED₁₀ 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.

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

⁸⁷ 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).

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 Regulation⁸⁸.

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 (Basketter et al., 1997)⁸⁹. 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 than those applied

⁸⁸ 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 $\geq 3\%$ in a mixture classified as Irrev Eye Effects 1 and $\geq 1\%$ but $< 3\%$ in mixtures classified as Cat. 2: Irritating to eyes (Eye Irrit. 2). The GCL for substances classified as Eye Effects 2 is $\geq 10\%$ in a mixture classified as Rev Eye Effects 2.

The GCL for substances classified as Skin Corr 1A/B/C is $\geq 5\%$ in a mixture classified as Skin Corr 1 and $\geq 1\%$ but $< 5\%$ in mixtures classified as Skin Irr 2. The GCL for substances classified as Skin Irr 2 is $\geq 10\%$ in a mixture classified as Skin Irr 2.

In addition to this, rules of addition apply.

⁸⁹ 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).

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in patch testing (Brockow et al., 2013)⁹⁰. 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 humans⁹¹ (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 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:

⁹⁰ 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.

⁹¹ 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).

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- 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 cm²
- Amount of ink⁹² injected to a person for a single 300 cm² full-colour tattoo:
 $300 \text{ cm}^2 \times 14.36 \text{ mg ink/cm}^2 = 4\,308 \text{ mg}$ (see previous section)
- Amount of ink injected per kg bw (60kg/person): 72 mg/kg bw/day
- Amount of the substance per kg bw:

$$72 \text{ mg/kg bw/day} \times C_{\text{substance in the ink}}$$

⁹² It should be noted that 4 308 mg ink applies to total mass of ink product, which contains both colourants and auxiliary ingredients.

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This value reflecting exposure of the person divided by DN(M)EL results in RCR:

$$RCR = \frac{\text{exposure}}{\text{DN(M)EL}} = \frac{72 \frac{\text{mg ink}}{\text{kg bw x d}}}{\text{DN(M)EL}} \times C_{\text{substance}} < 1$$

Therefore, when a DN(M)EL for an assessed substance is divided by this value, concentration limit ($C_{\text{substance}}$) for that substance is derived.

$$\text{Concentration limit of the substance in the ink} = \frac{\text{DN(M)EL substance} \frac{\text{mg}}{\text{kg bw x d}}}{72 \frac{\text{mg ink}}{\text{kg bw x d}}}$$

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:

$$\text{fraction of assessed substance in ink} * 4\,308 \text{ mg} / 60 \text{ kg bw}$$

This value divided by DN(M)EL results in RCR, while when a DN(M)EL for an assessed 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 2×10^{-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 4×10^{-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 concentration 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

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PAA has been proposed by the Dossier Submitter.⁹³ 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

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.⁹⁴

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 $0.05 \mu\text{g Pb/kg bw/d}$, which implies that a 60 kg person should maximally be injected with less than $3 \mu\text{g Pb/day}$ ($60 \text{ kg} \times 0.05 \mu\text{g Pb/kg/day}$) 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:

$$\text{Conc. limit Pb in ink} = \frac{0.00005 \frac{\text{mg}}{\text{kg bw} \times \text{d}}}{72 \frac{\text{mg ink}}{\text{kg bw} \times \text{d}}} = 0.00000069 \text{ mg Pb/mg ink} \approx 0.7 \text{ mg Pb/kg}_{\text{ink}} = 0.7 \text{ ppm}$$

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

⁹³ 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.

⁹⁴ 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.

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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 limit³⁷. 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 is calculated below.

Table 9 Derivation of concentration 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

$$(RCR) = \frac{\text{maximum injected dose (1730 } \mu\text{g Pb/d)}}{\text{maximum allowable dose of 3 } \mu\text{g Pb/d}} = 576.6$$

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:

$$2 \times 10^{-6} \text{ (max. permitted As concentration in ink, expressed as fraction}^{95}) \times 4\,308 \text{ mg ink} / 60 \text{ kg bw} = 0.0001436 \text{ mg As/kg bw (or } 0.144 \text{ } \mu\text{g As/kg bw)}$$

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:

$$6 \times 10^{-5} \text{ (maximum As concentration detected in ink, expressed as fraction}^{96}) \times 4\,308 \text{ mg ink} / 60 \text{ kg bw} = 0.0043 \text{ mg As/kg bw (or } 4.3 \text{ } \mu\text{g As/kg bw)}$$

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

⁹⁵ 2 mg/kg = 2 mg/1 000 000 mg = 0.000002 ppm = 2 x 10⁻⁶ppm

⁹⁶ 60 mg/kg = 60 mg/1 000 000 mg = 0.00006 ppm = 6 x 10⁻⁵ ppm

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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 lung cancer mortality risk is 1.7×10^{-3} per $\mu\text{g As/kg bw/day}$ (for oral route), and the excess lifetime lung cancer mortality risk due to arsenic exposure via tattooing could be estimated to:

$$1.7 \times 10^{-3} \times 0.1436 \mu\text{g As/kg bw} = 2.44 \times 10^{-4}$$

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 ($2.44 \times 10^{-4}/1 \times 10^{-6}$), 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

$$1.7 \times 10^{-3} \times 4.3 \mu\text{g As/kg bw} = 7.31 \times 10^{-3}$$

in the case of maximum arsenic concentration detected in ink (60 mg/kg), with resulting "RCR" of $>7\ 300$ ($7.31 \times 10^{-3} / 1 \times 10^{-6}$).

The Dossier Submitter concluded that the risk is not adequately controlled even at the maximum permitted level according to ResAP(2008)1⁹⁷ 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 **0.0000082%**).

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 (0.00005%) is supported by the range of concentration limits of 0.00002% to 0.00003% set

⁹⁷ 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).

for rice for adult EU population (Regulation EU 2015/1006)⁹⁸. 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 7×10^{-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:

$$0.024 \text{ (fraction of methanol in ink)} * 4 \text{ 308 mg (amount of ink injected in one session)} / 60 \text{ kg bw}$$

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.

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

⁹⁸ Concentration limits for rice for adults range from 0.00002% to 0.00003% according to Regulation EU 2015/1006.

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as Repr. 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}, 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:

$$\text{Concentration limit of the substance in the ink} = \frac{\text{DNEL substance} \frac{\text{mg}}{\text{kg bw x d}}}{72 \frac{\text{mg ink}}{\text{kg bw x d}}}$$

$$\text{Concentration limit for warfarin} = \frac{0.001 \frac{\text{mg substance}}{\text{kg bw x d}}}{72 \frac{\text{mg ink}}{\text{kg bw x d}}} = 0.0000139 = 13.9 \text{ mg}_{\text{subst}}/\text{kg}_{\text{ink}}$$

$$\text{CL} = 13.9 \text{ mg}_{\text{subst}}/\text{kg}_{\text{ink}} \text{ or } 13.9 \text{ ppm or rounded off to } 0.0014\%$$

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:

$$0.042\text{mg}/4308\text{mg} = 0.00000975 \text{ mg}_{\text{subst}}/\text{mg}_{\text{ink}} = 9.75 \text{ mg}_{\text{subst}}/\text{kg}_{\text{ink}} \approx 10\text{mg}_{\text{subst}}/\text{kg}_{\text{ink}} \\ = 10\text{ppm}$$

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:

$$\text{CL} = 10 \text{ mg}_{\text{subst}}/\text{kg}_{\text{ink}} \text{ or } 10 \text{ ppm or } 0.001\%$$

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 $\geq 0.3\%$ and as Category 2 reproductive toxicant $\geq 3\%$. 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:

$$36 \text{ mg Ba/day} / 4 \text{ 308 mg ink} = 0.0084 = 0.84\% \text{ w/w (8 400 ppm) soluble/dissolved Ba}$$

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:

$$2.4 \text{ mg Ba/day} / 4 \text{ 308 mg ink} = 0.00056 \approx \mathbf{0.05\% \text{ w/w}} \text{ soluble/dissolved Ba}$$

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 BaSO₄ 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)⁹⁹, 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:

$$1.1 \text{ mg Cu/day} / 4\,308 \text{ mg ink/day} \times 100\% = \mathbf{0.025\% \text{ of soluble Cu}}$$
 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 Zn²⁺ 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 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 cm²) is 4 308 mg ink per daily session (14.36 mg ink/cm² x 300 cm²).

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:

$$\text{Dose of zinc in worst case scenario} = 4\,308 \text{ mg ink} \times 0.17/100 = \mathbf{7.3 \text{ mg of Zn}^{2+} / \text{person}}$$

The risk to human health posed by Zn²⁺ 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:

$$\text{Risk} = \text{Exposure/DNEL} > 1$$

$$\text{RCR} = 7.3 \text{ mg}/10 \text{ mg} = 0.73 \text{ which is } < 1 \text{ and thus the risk is controlled}$$

Derivation of specific concentration limit for zinc

⁹⁹ This DNEL value is corrected for 50% oral absorption of copper in adult humans subjects with normal dietary copper intake (please see the section B.1.2.1.3).

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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 ($0.166 \text{ mg/kg bw} \times 60 \text{ kg} = 9.96 \text{ mg zinc}$) and that gives an amount of zinc in 100 mg of tattoo ink $10 \times 100/4308 = 0.23 \text{ mg} \approx 0.2 \text{ mg}$, 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.