Annex XV dossier

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

Substance Name(s): **o-Anisidine**

EC Number(s): **201-963-1**

CAS Number(s): **90-04-0**

Submitted by: Germany

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Substance Name(s): o-anisidine

EC Number(s): 201-963-1

CAS number(s): 90-04-0

- The substance is proposed to be identified as substance meeting the criteria of Article 57 (a) of Regulation (EC) 1907/2006 (EU, 2006; REACH Regulation) owing to its classification as carcinogen 1B[1] which corresponds to classification as carcinogen category 2[2].

Summary of how the substance meets the criteria as category 1B carcinogen.

o-Anisidine is covered by index number 612-035-00-4 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) as carcinogen, Carc. 1B (H350: "May cause cancer"). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is carcinogen, Carc. Cat. 2, R45 ("May cause cancer").

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

Registration dossiers submitted for the substance?

Yes

1 Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

2 Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC).

PART I

Justification

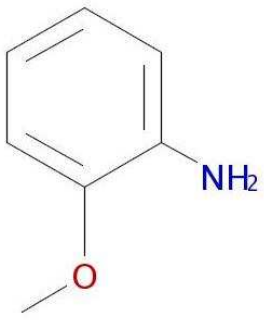
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	201-963-1
EC name:	o-anisidine
CAS number (in the EC inventory):	90-04-0
CAS number:	90-04-0
CAS name:	Benzenamine, 2-methoxy-
IUPAC name:	2-methoxybenzenamine
Index number in Annex VI of the CLP Regulation	612-035-00-4
Molecular formula:	C_7H_9NO
Molecular weight range:	123.15 g/mol

Structural formula:



1.2 Composition of the substance

Name: **o-anisidine**

Description: **mono-constituent substance**

Degree of purity: **> ca. 99 % w/w[3].**

Table 2 Constituents

Constituents	Typical concentration	Concentration range	Remarks
o-anisidine	> ca. 99 % w/w.		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Name and EC number			

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
Name and EC number			

Further details on the composition of the substance are confidential and can be found in the technical dossier.

[3] Based on the minimum typical content indicated in the registration dossiers (downloaded on 24/11/2010)

1.3 Physico-chemical properties

Table 5: Overview of physicochemical properties[4]

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	light red to yellow liquid (20°C, 1,013 hPa) with a faintly aromatic odor. It becomes brownish on exposure to air.	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Melting/freezing point	5 - >7 °C	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Boiling point	224 – 225 °C pressure not indicated	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Vapour pressure	0.02 - 0.05 hPa at 20 °C	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Water solubility	15 g/L at 20°C	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Partition coefficient n-octanol/water (log value)	log Kow 1.18 (measured) temperature not indicated	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Dissociation constant		
Density	1.0923 - 1.1 g/cm^3 at 20°C	Data from European Union Risk Assessment Report on o-anisidine (RAR, 2002)
Flash point	*107 °C (closed cup)*	CHEMSAFE (2009)
Flammability upon ignition (solids)	Testing can be waived, substance is a liquid.	BAM 2.2 (2011)
Flammability in contact with water	Testing can be waived in accordance with REACH Column 2 of Annex VII, 7.10, because the organic substance does not contain metals or metalloids.	BAM 2.2 (2011)
Pyrophoric properties	Testing can be waived in accordance with REACH Column 2 of Annex VII, 7.10, because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).	BAM 2.2 (2011)
Explosive properties	Testing can be waived in	BAM 2.2 (2011)

[4] *The references of the values reported in Table 5 will be available in the technical dossier.*

	accordance with REACH Column 2 of Annex VII, 7.11, because there are no chemical groups present in the molecule which are associated with explosive properties.	
Auto-ignition temperature (Liquids and Gases)	*430 °C (DIN 51794)*	CHEMSAFE (2009)
Oxidising properties	Testing can be waived in accordance with REACH Column 2 of Annex VII, 7.13, because the organic substance contains one oxygen atom which is chemically bonded only to carbon.	BAM 2.2 (2011)

2 HARMONISED CLASSIFICATION AND LABELLING

o-Anisidine is classified and labelled as follows:

Table 6: Classification and labelling according to Annex VI of Regulation (EC) 1272/2008, Table 3.1 (EU, 2008)

Index No	International Chemical Identification	Classification		Labelling			Specific Conc. Limits, M-factors
		Hazard Class and Category	Hazard Statement Code(s)	Pictogram, Signal Word	Hazard statement Code(s)	Suppl. Hazard statement Code(s)	
612-035-00-4	o-anisidine	Carc. 1B Muta. 2 Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 3 *	H350 H341 H331 H311 H301	GHS06 GHS08 Dgr	H350 H341 H331 H311 H301		

* minimum classification

Hazard statement codes:
H350: May cause cancer
H341: Suspected of causing genetic defects
H331: Toxic if inhaled
H311: Toxic in contact with skin
H301: Toxic if swallowed

Table 7: Classification and labelling according to Regulation (EC) 1272/2008, Table 3.2 (EU, 2008)

Index Number:	CAS No.	Classification	Labelling
612-035-00-4	90-04-0	Carc. Cat. 2; R45 Muta. Cat. 3; R68 T; R23/24/25	T R:45-23/24/25-68 S: 53-45

3 ENVIRONMENTAL FATE PROPERTIES

Since this is a dossier targeted to identification of o-anisidine as a CMR substance, environmental fate properties have not been considered.

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on harmonised classification and labelling.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Since this is a dossier targeted to identification o-anisidine as a CMR substance, no environmental hazard assessment has been carried out.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant for this dossier.

6.2 CMR assessment

o-Anisidine is covered by index number 612-035-00-4 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) as carcinogen, Carc. 1B (H350: “May cause cancer”). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is carcinogen, Carc. Cat. 2, R45 (“May cause cancer”).

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

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6.3 Substances of equivalent level of concern assessment.

Not relevant for this dossier.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

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

1.1 Information on Manufacture, Import/Export

o-Anisidine is produced by o-methylation of 2-nitrophenol followed by reduction of the nitro-group to the amino group. In 2010, o-anisidine has been registered as a transported isolated intermediate under strictly controlled conditions indicated in Article 18(4) of REACH legislation (EC) No. 1907/2006 with an aggregated volume between 1000 and 10 000 tonnes per year. There is no information on volumes of o-anisidine incorporated into imported articles.

1.2 Information on uses

According to some, but not all registration dossiers, o-anisidine is used for manufacture of dyes and as a processing aid. No further information on manufactured chemicals is given in the registration dossiers. Data on use for o-anisidine based chemicals are presented in the European Risk Assessment Report (RAR, 2002), according to which o-anisidine was used for a number of azo and naphthol pigments and dyes.

The main part of manufactured and imported o-anisidine in the EU was processed to azo pigments. These were mainly used in printing inks for packing materials like paper, cardboard, polymer and aluminum foil. 83 % was processed to yellow azo pigments (ordered by decreasing industrial importance): Pigment Yellow 74 (CAS No. 6358-31-2), Pigment Yellow 65 (CAS No. 6528-34-3), Pigment Yellow 17 (CAS No. 4531-49-1) and Pigment Yellow 73 (CAS No. 13515-40-7). 4 % was processed to red azo pigments: Pigment Red 15 (CAS No. 6410-39-5), Pigment Red 119 (CAS No. 61968-80-7 or 72066-77-4), Pigment Red 188 (CAS No. 61847-48-1), Pigment Red 261 (CAS No. 16195-23-6), Pigment Red 9 (CAS No. 6410-38-4). 13 % of o-anisidine with a decreasing tendency was processed to dyes for textiles (10 %), leather (0.1 %) and paper (3 %). The following dyes have to be considered as o-anisidine products: Acid Red 4 (CAS No. 5858-39-9), Acid Red 5 (CAS No. 5858-63-9), Acid Red 107 (CAS No. 6416-33-7), Acid Red 264 (CAS No. 6505-96-0), Basic Red 76 (CAS No. 68391-30-0), Acid Violet 12 (CAS No. 6625-46-3), Direct Yellow 118, Direct Yellow 120, Direct Yellow 132 (CAS No. 61968-26-1), Direct Red 24 (CAS No. 25188-08-3), Direct Red 26 (CAS No. 3687-80-7), Direct Red 72 (CAS No. 8005-64-9), Direct Red 123 (CAS No. 6470-23-1), and Food Red 16 (CAS No. 1229-55-6) (RAR, 2002).

Outside the EU, o-anisidine may be also used for the manufacture of guaiacol and vanillin (RAR, 2002).

1.2.1 Industrial uses

All registration dossiers declare industrial use of o-anisidine as an intermediate (PC 19) under strictly controlled conditions with no subsequent service life relevant for that use. Other use descriptors given in the dossiers are:

Process Categories:

- PROC 1: Use in closed process, no likelihood of exposure
- PROC 2: Use in closed, continuous processes with occasional controlled exposure
- PROC 3: Use in closed batch processes (synthesis or formulation)
- PROC 4: Use in batch and other processes (synthesis) where opportunity for exposure arises
- PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
- PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities

Environmental release categories:

- ERC 1: Manufacture of substances
- ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates)
- ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles

Sector of end use:

- SU 9: Manufacture of fine chemicals
- SU 0: Other: SU3: Industrial uses: Uses of substances as such or in preparations at industrial sites.

1.2.2 Professional use of o-anisidine

No professional use has been registered for o-anisidine.

With respect to the production of azo colorants that may contain o-anisidine it is unknown whether there pigments are intentionally produced for tattooing.

1.2.3 Consumer use

No consumer use has been registered for o-anisidine.

1.2.3.1 Consumer use of mixtures

o-Anisidine in mixtures for consumer use is restricted by entry number 28 Annex XVII of REACH Regulation (EU, 2006): Substances which appear in Part 3 of Annex VI of Regulation (EC) No 1272/2008 classified as carcinogen category 1A or 1B (Table 3.1) or carcinogen category 1 or 2 (Table 3.2) shall not be placed on the market, or used, as substances, as constituents of other substances, or, in mixtures for supply to the general public when the individual concentration in the

substance or mixture is equal or greater than either the relevant specific concentration limit specified in Part 3 of Annex VI of Regulation (EC) No 1272/2008, or the relevant concentration specified in Directive 1999/45/EC. According to Directive 1999/45/EC the specific concentration limit is 0.1 %.

Nevertheless, o-anisidine has occasionally been found in mixtures for consumer use, e.g. in a crayon for children (Öko-Test, 2006) (concentration not given, the analytical method was declared to be different from standard procedures for toys) and in a yellow azo colorant from a toner (Computer Bild, 2008) (analysis according to DIN EN 14362). o-Anisidine was also detected at a concentration of 1.8 % (w/w) in a powdered color for do-it-yourself candle production. It derived from 4 % Solvent Red 18 (C.I. No. 12150), which had not been declared as constituent of the mixture. As a consequence, the producer recalled this color from the market (CVUA, 2002).

1.2.3.2 Consumer use of tattoo inks containing o-anisidine

This special use may result in a considerable exposure of the general population to o-anisidine.

Tattooing is a process, in which substances or preparations are administered into skin or subcutis to influence its appearance permanently. Tattooing includes decorative tattoos and permanent make-up (PMU). The number of Europeans getting tattooed has been increased during the last years (Klügl et al., 2010). During tattooing colorants with contents of pigment up to 40 % are injected under the skin (Engel et al., 2008 a). Pigments used for tattooing can also include azo dyes, which may cleave into carcinogenic aromatic amines. An azo pigment based on o-anisidine, which is commonly used for tattooing is Pigment Yellow 74 (C.I. 11471, CAS No. 6358-31-2).

In colorants for tattooing, o-anisidine can be an impurity or also a cleavage product of the corresponding organic pigments. UV-radiation and skin bacteria may facilitate the degradation of azo dyes and thereby the formation of o-anisidine (Engel et al., 2009 and 2007, Cui et al., 2004). Additionally, metabolic processes in the skin may play a role in cleaving azo dyes into aromatic amines (Cui et al., 2005). If present, o-anisidine as an impurity in tattoo inks becomes biologically available directly after application of the ink.

The Council of Europe adopted resolutions recommending regulation of tattoo colorants in national laws ResAP (2003) 2, ResAP (2008) 1. In Germany a national legislation (TätVO, 2008) bans the use of azo colorants, which are cleaved to aromatic carcinogenic amines listed in Annex I of the legislation. A national ban on the use of azo dyes in tattoo inks has also been adopted by the Netherlands (Warenwetbesluit tatoeagekleurstoffen, 2003). But of the majority of European Member States do not yet have any regulation on tattoo colorants.

In 2007, o-anisidine has been detected in three tattoo inks in the Netherlands in concentrations of 1130 mg/kg, 374 mg/kg and 344 mg/kg (RAPEX, 2007) and also in another tattoo ink in Germany (LUA, 2007). In 2010, authorities in the Netherlands investigated 138 samples of tattoo ink for release of aromatic amines after reductive cleavage (table 6). In 27 (20 %) of these samples o-anisidine was determined (detection limit: 10 mg/kg). Concentrations ranged from 16 to 1490 mg/kg (VWA, 2011).

Table 8: Concentration ranges of aromatic amines in 138 tattoo inks

Concentration range (mg/kg)	Number of samples
< 10	111
10-100	8
100-500	5
500-1000	11
> 1000	3

Due to the low numbers of samples taken by VWA in the Netherlands the concentration values may not be representative for the tattoo colors applied to the general population in Europe. The market in the Netherlands may be influenced by the Dutch regulation on the use of azo colorants in tattoo colors that potentially release of carcinogenic amines. Even higher numbers of azo colorants that deliver or contain o-anisidine can be assumed to be detected in other Member States lacking a regulation on tattoo inks.

Based on the measure concentrations, the 95th percentile of the values lies between 500 and 1000 mg/kg. Therefore, an o-anisidine concentration of 750 mg/kg is taken forward for a reasonable worst case assessment of the potential amount of o-anisidine introduced into the skin by o-anisidine based tattoo inks. The mean value of about 100 mg/kg is used for the corresponding average case assessment.

The amounts of tattoo pigment injected into the skin during tattooing were determined in an ex vivo pig skin model and in human skin samples from skin biopsies (Engel et al., 2008a). Researchers tattooed 14 triple with different tattoo machines and commercial or synthesized pigment Pigment Red 22. In the pig skin model Pigment Red 22 content was between 0.63 and 2.90 mg/cm² for 10% pigment solutions and between 1.42 and 9.42 mg/cm^2 for 25% pigment solutions. Two samples of human skin biopsies were tattooed with 25% pigment solutions resulting in injected amounts of 0.95 and 1.69 mg/cm². The median from the pig skin experiments with 25% pigment solutions is 3.5 mg/cm². This value is taken forward for the reasonable worst case assessment. In the same study, professional tattoo artists tattooing a triple sample of pigskin with their own equipment and 25% pigment injected an average amount of 0.6 mg/cm². This value is taken forward for the average case assessment. Amounts of o-anisidine based tattoo pigments are supposed to be similar.

Based on these values, the intradermal load as the potential amount of o-anisidine injected into skin is 10.5 µg/cm² in the reasonable worst case and 0.24 µg/cm² in the average case (table 7).

Table 9: Estimation of the intradermal load of o-anisidine from tattoo inks

Model					**Source**
$L_{intradermal} = C_{s/i} / C_{p/i} \times C_{p/A} \times K$					
Input parameter	**Description**	**Reasonable Worst Case Value**	**Average Case Value**	**Unit**	
$C_{s/i}$	Concentration of substance in tattoo ink	750	100	[mg/kg]	VWA (2011)
$C_{p/i}$	Concentration of pigment in tattoo ink	0.25	0.25	[mg/mg]	Engel et al (2008a)
$C_{p/A}$	Concentration of pigment per tattooed area	3.5	0.6	[mg /cm²]	Engel et al. (2008a)
K	Conversion factor	1/1000	1/1000		
Output parameter	**Description**				
$L_{intradermal}$	Intradermal load	10.5	0.24	[µg / cm²]	

The potential o-anisidine dose of a tattooed person can be calculated combining the intradermal load with the tattooed area. In an internet survey with 3411 participants from German speaking countries (Klügl et al., 2010), 28% had 4 tattoos or more and 36% reported the latest one to have a size of 900 cm² or more. Based on these data, 5 tattoos of 900 cm² are taken forward for a reasonable worst case assessment and two tattoos of 300 cm² are used for the average case estimation.

In the reasonable worst case, a person with 60 kg body weight could be tattooed with 5 tattoos, each of which had 900 cm² of size. An intradermal load of 10.5 µg o-anisidine per cm² would result in a potential dose of 787.5 µg o-anisidine per kg body weight (table 8).

In the average case, a person with 60 kg body weight could be tattooed with two tattoos of 300 cm² size. An intradermal load of 0.24 µg o-anisidine per cm² would result in a potential dose of 2.4 µg o-anisidine per kg body weight (table 8).

Table 10: Estimation of the potential dose of o-anisidine from tattoo inks

Model					**Source**
$D = L_{intradermal}$ x n x A / BW					
Input parameter	**Description**	**Reasonable Worst Case Value**	**Average Case Value**	**Unit**	
$L_{intradermal}$	Potential intradermal load	10.5	0.24	[µg / cm²]	See table 7
N	Number of tattoos	5	2		Klügl et al. (2010)
A	Tattoo size	900	300	[cm²]	Klügl et al. (2010)
BW	Body weight	60	60	[kg]	ECHA (2010)
Output parameter	**Description**				
D	Potential dose	787.5	2.4	[µg / kg]	

Calculated doses are to be regarded as potential doses for reasonable worst case and average case exposures. Uncertainties in the reductive cleavage from the azo colorants have influence on the intradermal load and might result in an overestimation.

The size of the tattooed areas communicated in the internet survey may not be representative for the tattooed population as tattooed people may be especially interested in tattooing. No representative data on tattoo areas were found, but the internet survey by Klügl et al. (2010) is considered to reveal realistic exposure conditions of a population at risk. However, some people have tattooed almost the complete body surface. In the extreme case of a woman who had her body almost completely tattooed (except her head and the palms of hands and feet), a tattooed body area of 15000 cm² (ECHA, 2010) with an intradermal load of 10.5 µg/cm² corresponds to an o-anisidine dose of 2625 µg per kg body weight.

Transport to other tissues

Dye pigments from tattooing are largely stored intracellularly in subcutaneous cells from where they may also be transported via blood vessels and lymph passages to other sites and organs (such as lymph nodes) of the body. Cases of skin cancer arising in tattooed areas were reported, however, the role of tattooing colorants in the pathogenesis of skin cancer is still unclear (Engel et al., 2008 b; Kluger et al., 2008; West et al., 2009). In tattooed patients with melanoma, the pigments were also found in the lymph nodes (Rozen and Nahabedian, 2004; Dominguez et al., 2008; Peterson et al., 2008). Using a nude mouse model it was demonstrated that 42 days after application pigment concentration in the skin was reduced by 32 %. When the animals were also exposed to sunlight or laser radiation, the pigment concentration in the skin was reduced by 60 % and 51 %, respectively (Engel et al., 2009).

1.2.3.3 Consumer use of textile and leather articles

o-Anisidine is listed by Annex XVII of REACH Regulation entry number 43 (EU, 2006): 'Azodyes which, by reductive cleavage of one or more azo groups, may release one or more of the aromatic amines listed in Appendix 8, in detectable concentrations, i.e. above 30 ppm in the finished articles or in the dyed parts thereof, …, shall not be used in textile and leather articles which may come into direct and prolonged contact with the human skin or oral cavity, ...'. o-Anisidine is one of the listed amines in Appendix 8.

Compliance to these limit values has been evaluated in two studies: 9.7 % from 155 textile and leather samples analyzed by German authorities released aromatic amines in concentrations above 30 ppm (Krätke and Platzek, 2005). In a coordinated surveillance project by 9 European Member States, 369 textile and leather samples and two dyes were analyzed, and 2.5 % of the samples released aromatic amines in concentrations above 30 ppm (EurAzos, 2007).

Danish EPA (2009) reported o-anisidine concentrations in bed linen of 4.5 µg/g (before standard washing) and 8 µg/g (after washing). The results of the analyses are semiquantitative since the substances were estimated according to internal standards. Assuming, that all o-anisidine contained in the linen would be absorbed by a 2-year old child with 10.3 kg body weight by dermal contact, Danish EPA calculated a TIER 1 exposure of 1.3 µg/kg bodyweight.

1.2.3.4 Consumer use of paper articles

o-Anisidine based azo colorants are used in printing inks for paper articles like books, packings, wallpapers (RAR, 2002). According to the main German producer of o-anisidine in 1997, pigments used for printing inks contained between 10 and 50 ppm o-anisidine. Based on these data, a calculation of the German Printing Industry presented in the European Risk Assessment Report (RAR, 2002) resulted in o-anisidine amounts between 0.012 and 0.12 mg per m² paper and between 0.02 and 0.2 mg per kg paper. No exposure calculations were performed for this source in the RAR.

Dermal exposure from use of a coloured folder of paper with an o-anisidine concentration of 257 µg/g was assessed by RIVM (2000) resulting in 7 - 28 ng o-anisidine per day.

1.2.3.5 Consumer use of plastic and rubber articles

o-Anisidine may be a constituent of dyed and printed polymers, and especially in printed packing foils. Based on an o-anisidine content of 10 to 50 ppm in printing pigments, a calculation of the German Printing Industry presented in the European Risk Assessment Report (RAR, 2002) resulted in o-anisidine amounts between 1.5 and 15 µg per m² foil.

1.2.3.6 Consumer use of metal articles

o-Anisidine may be a component in painted and printed metal articles, and especially in printed aluminum foils. Based on an o-anisidine content of 10 to 50 ppm in printing pigments, a calculation of the German Printing Industry presented in European Risk Assessment Report (RAR, 2002) resulted in o-anisidine amounts between 1.5 and 15 µg per m² foil.

1.2.3.7 Consumer uses not covered by the REACH regulation

Cosmetics

In the Cosmetics Directive 76/768/EEC, o-anisidine is listed in Annex II as a substance, which must not form part of the composition of cosmetic products. Solvent Red 1, CAS No. 1229-55-6, is known to release o-anisidine (Platzek et al., 2005), and use of Solvent Red 1 in hair colorants has been banned by Commission Directive 2006/65/EC of 19 July 2006 amending Council Directive 76/768/EEC.

Food contact materials

o-Anisidine is not mentioned in the positive lists for food contact materials. Commission Directive, 2002/72/EC establishes that plastic material and articles shall not release primary aromatic amines in a detectable quantity (detection limit: 0.1 mg/kg of food or food simulant). This limit includes possible migration of o-anisidine. Migration of o-anisidine to food caused by residues in colorants for dying or printing or by colorant degradation cannot be excluded. No measured data on o-anisidine migration into food have been found.

Tobacco smoke

o-Anisidine has been detected in mainstream cigarette smoke in concentrations between 0.41 and 5.1 ng/cigarette (LGL, 2006). While Weiss and Angerer (2004) did not detect any significant correlation between cotinine excretion as an internal marker for smoking status and o-anisidine excretion in urine, Kütting et al. (2009) found a weak but significant difference in o-anisidine excretion of smokers and non-smokers (table 9).

1.3 Human Biomonitoring Data

Biomonitoring data on o-anisidine exposure in the general population are summarized in table 9.

o-Anisidine was reported in urine samples at concentrations up to 8.66 ng/ml urine with median values of 0.2-0.3 ng/ml urine. Sources of o-anisidine origin are hardly to estimate. Only the study of Kütting et al. (2009) who reported significant higher values for smokers could be interpreted to allow assumptions that smoking behaviour may correspond to higher o-anisidine concentrations.

Table 11: Human biomonitoring data on o-anisidine in the general population

Biomarker	Location	Study population	N	LOD (ng/ml)	%>LOD	Median (ng/ml)	Mean (ng/ml)	Min (ng/ml)	Max (ng/ml)	95. P (ng/ml)	Study
o-anisidine in urine	Germany	People without known exposure	20	0.05	95	0.22		<LOD	4.2	0.68	Weiss and Angerer, 2002
o-anisidine in urine	Germany	Total population, 20 – 73 years	197	0,05	97.5	0.268		<LOD	1.394	0.715	Weiss and Angerer, 2004
		Rural population, 20 – 68 years	99	0,05	96.0	0.266		<LOD	1.394	0.567	
		Urban population, 22 – 73 years	98	0,05	99.0	0.273		< LOD	1.272	0.722	
o-anisidine in urine	Germany	General population, 3 – 84 years	1004	0.05	90.0	0.23	0.37	<LOD	8.66	1.12	Kütting et al., 2009
		Smoker	145	0.05	95.8	0.29	0.4	<LOD	4.04	1.24	
		Non-smoker	856	0.05	89.0	0.21	0.36	<LOD	8.66	1.04	
		Female	592	0.05	86.9	0.19	0.32	<LOD	6.98	0.93	
		Male	411	0.05	94.4	0.3	0.45	<LOD	8.66	1.29	

Sample	Location	Study population	N	LOD (ng/L)	%>LOD	Median (ng/L)	Mean (ng/L)	Min (ng/L)	Max (ng/L)	95. P (ng/L)	Study
Hemoglobine adducts of o-anisidine in blood	Germany	Total population, 20 – 73 years	156	0.5	89.4	2.1		<LOD	4500	16	Weiss and Angerer, 2004

N = sample size

LOD limit of detection

2 ALTERNATIVES

Due to the existing restrictions, o-anisidine based colorants have been widely substituted by alternatives in the cosmetic sector and in textile and leather articles which may come into direct and prolonged contact with the human skin or oral cavity. Substitution of o-anisidine based colorants in tattoo inks according to resolutions of the European Council (ResAP (2003) 2 and ResAP (2008) 1) has been issued by national laws in several but not all European Member States. A German laboratory has compiled a database of tattoo- and permanent make-up products which comply with the EU ResAP(2008)1 (CTL, 2011), and there may be other similar compilations from other laboratories.

In addition, the European Printing Ink Association has published a voluntary exclusion list for printing inks and related products, which also includes 'Other soluble azo dyes which can decompose in the body to bio-available carcinogenic aromatic amines of category 1 and 2 according to Directive 67/548/EEC' (EUPIA, 2011). Industry's voluntary abandonment indicated that there are suitable alternatives to o-anisidine releasing colorants in printing inks.

3 RISK-RELATED INFORMATION

In view of the carcinogenic properties of o-anisidine (genotoxic carcinogen without threshold), consumer exposure to this substance should be as low as reasonably achievable. While risks resulting from exposure to the substance itself, to mixtures and to dyed textiles and leather articles which may come into direct and prolonged contact with the human skin or oral cavity are controlled by existing restrictions in Annex XVII of the REACH Regulation, risks resulting from o-anisidine in other imported articles are still possible. At present, data are limited giving evidence on o-anisidine content in consumer articles.

Moreover, release of o-anisidine from o-anisidine based tattoo pigments may result in a considerable risk for the general population. At present, this risk can not be fully evaluated because little is known about the amounts and kinetics of o-anisidine releases from azo pigments after their injection into the skin and in the case of tattoo removal by laser radiation.[5]

OVERALL CONCLUSION

o-Anisidine fulfils the SVHC criteria laid down under Article 57 (a) of the REACH Regulation (EU, 2006). The inclusion of o-anisidine in the Candidate List is a supplementary action to limit consumer risks from o-anisidine from all sources and a relevant risk management option even without subsequent inclusion in Annex XIV.

Due to the obligation of producers and importers to notify SVHC from the Candidate List in articles (Art. 7 (2a, b)), available information about the uses of o-anisidine may increase. Moreover, consumers may take their right of requesting information on articles containing o-anisidine

[5] Preliminary considerations to prepare a restriction of tattoo inks containing or releasing carcinogenic amines are ongoing.

according to Art. 33 of the REACH Regulation. Hence the right of consumers to get more information on o-anisidine will be strengthened.

In addition, the public consultation process on risks from o-anisidine based tattoo pigments may help to clarify the supply chain for this special use and produce a signal effect to consumers who consider getting tattooed.

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