HMA
Heads of Medicines Agencies

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP

(HMPWG)

1ST LIST OF FIRST SAFE DILUTIONS (FSD)

DISCUSSION IN THE FSD-SUBGROUP	23 - 24 February 2016
DISCUSSION IN THE HMPWG	14 – 15 April 2016
ADOPTION BY THE HMPWG for public consultation	May 2016
TRANSMISSION TO HMA for release for consultation	May 2016
DEADLINE FOR COMMENTS	27 August 2016
DISCUSSION IN THE FSD-SUBGROUP	4 October 2016
ADOPTION BY THE FSD-SUBGROUP	24 October 2016
DISCUSSION IN HMPWG and Adoption	10 - 11 November 2016

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Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Acidum arsenicosum **As_2O_3** HAB	Ph. Eur. 3.1.1 (HAB 5a) Ph. Eur. 4.1.2 (Ph. Franç.)	As_2O_3: 0.95 - 1.06 % in D2 M_r = 197.84 Relative content As in stock = 75.76 %	PDE	0.3 µg As/kg/day → 0.9 µg As/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D2 = 106 mg As_2O_3 = 80.31 mg As → 10 g D7 = 0.8031 µg As	**D7**	For derivation of PDE see ICH Q3D. Derivation of PDE arsenic: MRL = 0.0003 mg As/kg/d x 3 kg bw neonate ⟶ 0.9 µg As/d (no UF).
Allium cepa Ph. Franç.	Ph. Eur. 1.1.10 (Ph. Franç.)	N/A	Allowed daily intake	50 g	Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) claiming an increase in renal water elimination, "kidneys health", "urinary health", "bladder health", "health of lower urinary tract", "blood health", "elimination", "urinary system benefits" and/or "supports/promotes the excretory function of the kidney", and treatment/prevention of renal gravel/kidney stones and urinary tract infections pursuant to Article 13(1) of Regulation (EC) No 1924/20061 (EFSA Journal 2010; 8(10):1742)	·/·	**MT**	

1	2	3	4	5	6	7	8	9
Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Allium cepa HAB	Ph. Eur. 1.1.3 (HAB 2a)	N/A	Allowed daily intake	50 g	Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) claiming an increase in renal water elimination, "kidneys health", "urinary health", "bladder health", "health of lower urinary tract", "blood health", "elimination", "urinary system benefits" and/or "supports/promotes the excretory function of the kidney", and treatment/prevention of renal gravel/kidney stones and urinary tract infections pursuant to Article 13(1) of Regulation (EC) No 1924/20061 (EFSA Journal 2010; 8(10):1742)	·/·	**MT**	
Arsenum iodatum **AsI_3** HAB	Ph. Eur. 3.1.1 (HAB 5a)	AsI_3: 0.95 - 1.05 % in D2 M_r = 455.6 Relative content As in stock = 16.44 %	PDE	0.3 µg As/kg/day → 0.9 µg As/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D2 = 105 mg AsI_3 = 17.26 mg As → 10 g D7 = 0.1726 µg As	**D7**	For derivation of PDE see ICH Q3D. Derivation of PDE arsenic: MRL = 0.0003 mg As/kg/d x 3 kg bw neonate → 0.9 µg As/d (no UF).
Arsenicum iodatum **AsI_3** Ph. Franç.	Ph. Eur. 4.1.2 (Ph. Franç.)	AsI_3: 97.0 - 101.0 % in stock M_r = 455.6 Relative content As in stock = 16.44 %	PDE	0.3 µg As/kg/day → 0.9 µg As/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D2 = 101 mg AsI_3 = 16.604 mg As → 10 g D7 = 0.166 µg As	**D7**	For derivation of PDE see ICH Q3D. Derivation of PDE arsenic: MRL = 0.0003 mg As/kg/d x 3 kg bw neonate → 0.9 µg As/d (no UF).

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Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Atropa belladonna HAB	Ph. Eur. 1.1.3 (HAB 2a): D1 = 2 MT + 8 ethanol	Alkaloids: hyoscyamine: 0.02 - 0.05 % in MT → 10 g MT = 5 mg alkaloids	LHRD/100	0.6 µg atropine/day (neonate)	Merck Manual (as from 22/11/2010)	10 g MT = 5 mg alkaloids → 10 g D5 = 0.1 µg alkaloids	**D5**	Dosage for children < 5 kg = 0.02 mg/kg = 0.06 mg/3 kg neonate → divided through 100 = 0.6 µg/3 kg neonate/day.
Atropa belladonna Ph. Eur.	Ph. Eur. 1.1.10 (Ph. Franç.)	Alkaloids: hyoscyamine: 0.02 - 0.05 % in MT → 10 g MT = 5 mg alkaloids	LHRD/100	0.6 µg atropine/day (neonate)	Merck Manual (as from 22/11/2010)	10 g MT = 5 mg alkaloids → 10 g D4 = 0.5 µg alkaloids	**D4**	Dosage for children < 5 kg = 0.02 mg/kg = 0.06 mg/3 kg neonate → divided through 100 = 0.6 µg/3 kg neonate/day.
Berberis vulgaris HAB	Ph. Eur. 1.1.8 (HAB 4a): MT = D1	Berberine: 0.18 - 0.60 % in MT → 10 g MT (D1) = 60 mg berberine	PDE	0.45 mg berberine/kg/day → 1.35 mg berberine/day (neonate)	Jahnke GD, Price CJ, Marr MC, Myers CB, George JD.Developmental toxicity evaluation of berberine in rats and mice. Birth Defects Res B Dev Reprod Toxicol. 2006;77(3):195-206.	10 g MT (D1) = 60 mg berberine → 10 g D3 = 0.6 mg berberine	**D3**	Derivation of PDE berberine: NOAEL rat = 223 mg berberine/kg divided by UF (F1-F5 = 5 x 10 x 10 x 1 x 1) = 0.45 mg berberine/kg/day
Berberis vulgaris Ph. Franç.	Ph. Eur. 1.1.10 (Ph. Franç.)	Berberine: 0.10 - 0.30 % in MT → 10 g MT = 30 mg berberine	PDE	0.45 mg berberine/kg/day → 1.35 mg berberine/day (neonate)	Jahnke GD, Price CJ, Marr MC, Myers CB, George JD.Developmental toxicity evaluation of berberine in rats and mice. Birth Defects Res B Dev Reprod Toxicol. 2006;77(3):195-206.	10 g MT = 30 mg berberine → 10 g D2 = 0.30 mg berberine	**D2**	Derivation of PDE berberine: NOAEL rat = 223 mg berberine/kg divided by UF (F1-F5 = 5 x 10 x 10 x 1 x 1) = 0.45 mg berberine/kg/day

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Stock* /raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Chelidonium majus HAB	Ph. Eur. 1.1.5 (HAB 3a): D1 = 3 MT + 7 ethanol	MT: maximum 0.20 % of alkaloids, calculated as chelidonine → 10 g MT = 20.0 mg alkaloids	TTC	0.15 µg/day	HMPWG - Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (2007)	10 g MT = 20.0 mg alkaloids → 10 g D6 = 0.060 µg alkaloids	**D6**	Rationale for TTC-approach: • toxicity concern • limited data • exclusions considerations not applicable
Chelidonium majus Ph. Franç	Ph. Eur. 1.1.10 (Ph. Franç.)	MT: maximum 0.050 % of alkaloids, calculated as chelidonine → 10 g MT = 5 mg alkaloids	TTC	0.15 µg/day	HMPWG - Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (2007)	10 g MT = 5 mg alkaloids → 10 g D5 = 0.05 µg alkaloids	**D5**	Rationale for TTC-approach: • toxicity concern • limited data • exclusions considerations not applicable
Cr^{6+}	Stock = chemical substance	10 g stock = 10 g Cr^{6+}	PDE	parenteral PDE: 0.5 µg Cr^{6+}/kg/day → 1.5 µg Cr^{6+}/day (neonate)	Guideline on specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000)	10 g D7 = 1.0 µg Cr^{6+}	**D7**	Preparations applied as a spray shall be assessed on the basis of the inhalation PDE for hexavalent chromium (= 10 ng/day). For derivation of PDE see EMEA/CHMP/SWP/4446/2000 and RIVM Report 711701025, respectively. Due to the toxicity of hexavalent chromium and a possible high bioavailability of the active substance in the case of a sublingual application, as a conservative approach the parenteral PDE was chosen.

1	2	3	4	5	6	7	8	9
Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Hydrargyrum biiodatum **HgI_2** HAB See Mercurius bi-iodatus	Ph. Eur. 3.1.1 (HAB 5a)	HgI_2: 0.094 - 0.110 % in D3 M_r = 454.4 Relative content Hg in stock = 44.14 %	PDE	0.6 µg Hg/kg/day → 1.8 µg Hg/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D3 = 11 mg HgI_2 = 4.86 mg Hg → 10 g D7 = 0.486 µg Hg	**D7**	For derivation of PDE see ICH Q3D. Derivation of PDE mercury: $BMDL_{10}$ 0.06 mg Hg/kg/day divided by UF (F1-F5 = 5 x 10 x 2 x 1 x 1) → 0.0006 mg Hg/kg/d x 3 kg bw neonate → 0.0018 mg Hg/d = 1.8 µg Hg/d
Kalium bichromicum **$K_2Cr_2O_7$** HAB	Ph. Eur. 3.1.1 (HAB 5a)	$K_2Cr_2O_7$: 0.94 - 1.07 % in D2 M_r = 294.2 Relative content of Cr^{6+} in stock = 35 %	PDE	parenteral PDE: 0.5 µg Cr^{6+}/kg/day → 1.5 µg Cr^{6+}/day (neonate)	Guideline on specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000)	10 g D2 = 107 mg $K_2Cr_2O_7$ = 37.45 mg Cr^{6+} → 10 g D7 = 0.3745 µg Cr^{6+}	**D7**	Preparations applied as a spray shall be assessed on the basis of the inhalation PDE for hexavalent chromium (= 10 ng/day). For derivation of PDE see EMEA/CHMP/SWP/4446/2000 and RIVM Report 711701025, respectively. Due to the toxicity of hexavalent chromium and a possible high bioavailability of the active substance in the case of a sublingual application, as a conservative approach the parenteral PDE was chosen.

1	2	3	4	5	6	7	8	9
Stock* /raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Kalium stibyltartaricum **$C_8H_4K_2O_{12}Sb_2 \cdot 3H_2O$** HAB	Monograph specific preparation (HAB): D2 = 1 part raw material + 84 parts water + 15 parts ethanol D3 = 1 part D2 + 9 parts ethanol	$C_8H_4K_2O_{12}Sb_2 \cdot 3H_2O$: 0.95 - 1.05 % in D2 M_r = 668 Relative content Sb in stock = 36.4 %	PDE	24 µg Sb/kg/day → 72 µg Sb/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D2 = 105 mg raw material = 38.22 mg Sb → 10 g D5 = 38.22 µg Sb	**D5**	For derivation of PDE see ICH Q3D. Derivation of PDE antimony: NOAEL 6000 µg Sb/kg/d divided by UF (F1-F5 = 5 x 10 x 5 x 1 x 1) = 24 µg Sb/kg/d x 3 kg bw neonate = 72 µg Sb/d
Mercurius bi-iodatus **HgI_2** Ph. Franç. See Hydrargyrum biiodatum	Ph. Eur. 4.1.2 (Ph. Franç.)	HgI_2: minimum 99.0 % in stock Relative content Hg in stock = 44.14 %	PDE	0.6 µg Hg/kg/day → 1.8 µg Hg/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D3 = 10 mg HgI_2 = 4.414 mg Hg → 10 g D7 = 0.4414 µg Hg	**D7**	For derivation of PDE see ICH Q3D. Derivation of PDE mercury: $BMDL_{10}$ 0.06 mg Hg/kg/day divided by UF (F1-F5 = 5 x 10 x 2 x 1 x 1) → 0.0006 mg Hg/kg/d x 3 kg bw neonate → 0.0018 mg Hg/d = 1.8 µg Hg/d
Plumbum metallicum **Pb** HAB	Ph. Eur. 4.1.1 (HAB 6) Ph. Eur. 4.1.2 (Ph. Franç.) Stock = chemical substance	Pb: 9.4 - 10.6 % in D1	PDE	5 µg Pb/day (neonate)	ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)	10 g D1 = 1.06 g Pb → 10 g D7 = 1.06 µg Pb	**D7**	For derivation of PDE see ICH Q3D. Derivation of PDE lead: Oral intake of 5 µg lead/day translates into a blood level of 1-2 µg lead/dL established from epidemiological studies for children age 0-7 years (0-82 months)

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Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Sanguinaria canadensis Ph. Franç.	Ph. Eur. 1.1.10 (Ph. Franç.)	Alkaloids: sanguinarine chloride: 0.10 - 0.30 % in MT → 10 g MT = 30 mg sanguinarine chloride	PDE	16 µg sanguinarine chloride/kg/day → 48 µg sanguinarine chloride(sanguinaria alkaloids)/day (neonate)	International Research and Development Corporation: Thirteen-Week Oral Toxicity Study in Cynomolgus Monkey, Sept. 21, 1988; cited in the FDA MONOGRAPH as: Thirteen-Week Oral Toxicity Study in Cynomolgus Monkeys, unpublished study VS-143 in OTC Vol. 210306	10 g MT = 30 mg sanguinarine chloride → 10 g D3 = 30 µg sanguinarine chloride	**D3**	Derivation of PDE sanguinarine: NOAEL 10 mg sanguinarine chloride/kg divided by UF (F1-F5 = 3 x 10 x 10 x 1 x 2 = additional modifying factor of 2 due to date of data) = 0.016 mg sanguinarine chloride/kg/d = 16 µg sanguinarine chloride/kg/day x 3 kg bw neonate = 48 µg sanguinarine chloride/d
Sanguinaria canadensis HAB	Ph. Eur. 1.1.8 (HAB 4a): MT = D1	Alkaloids, calculated as chelidonine: 0.20 - 0.50 % in MT → 10 g MT (= D1) = 50 mg alkaloids	PDE	16 µg sanguinarine chloride/kg/day → 48 µg sanguinarine chloride (sanguinaria alkaloids)/day (neonate)	International Research and Development Corporation: Thirteen-Week Oral Toxicity Study in Cynomolgus Monkey, Sept. 21, 1988; cited in the FDA MONOGRAPH as: Thirteen-Week Oral Toxicity Study in Cynomolgus Monkeys, unpublished study VS-143 in OTC Vol. 210306	10 g MT (= D1) = 50 mg alkaloids → 10 g D5 = 5 µg alkaloids	**D5**	Derivation of PDE sanguinarine: NOAEL 10 mg sanguinarine chloride/kg divided by UF (F1-F5 = 3 x 10 x 10 x 1 x 2 = additional modifying factor of 2 due to date of data) = 0.016 mg sanguinarine chloride/kg/d = 16 µg sanguinarine chloride/kg/day x 3 kg bw neonate = 48 µg sanguinarine chloride/d

1	2	3	4	5	6	7	8	9
Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Sanguinaria canadensis, ethanol. Decoctum HAB	HAB 19f: MT = D1	Alkaloids, calculated as chelidonine: 0.20 - 0.50 % in MT → 10 g MT (= D1) = 50 mg alkaloids	PDE	16 µg sanguinarine chloride/kg/day → 48 µg sanguinarine chloride (sanguinaria alkaloids)/day (neonate)	International Research and Development Corporation: Thirteen-Week Oral Toxicity Study in Cynomolgus Monkey, Sept. 21, 1988; cited in the FDA MONOGRAPH as: Thirteen-Week Oral Toxicity Study in Cynomolgus Monkeys, unpublished study VS-143 in OTC Vol. 210306	10 g MT (= D1) = 50 mg alkaloids → 10 g D5 = 5 µg alkaloids	**D5**	Derivation of PDE sanguinarine: NOAEL 10 mg sanguinarine chloride/kg divided by UF (F1-F5 = 3 x 10 x 10 x 1 x 2 = additional modifying factor of 2 due to date of data) = 0.016 mg sanguinarine chloride/kg/d = 16 µg sanguinarine chloride/kg/day x 3 kg bw neonate = 48 µg sanguinarine chloride/d
Strychnos nux-vomica Ph. Eur.	Ph. Eur. 1.1.8 (HAB 4a): MT = D1	Indole alkaloids: 0.15 - 0.30 % in MT, thereof 43 - 67 % strychnine → 10 g MT = 30 mg indole alkaloids = 20.1 mg strychnine	RfD	300 ng strychnine/kg/day → 0.9 µg strychnine/day (neonate)	US EPA Integrated Risk Information System: Strychnine. The RfD is calculated on the basis of the study from Seidl and Zbinden, 1982; Subchronic oral toxicity of strychnine in rats. Arch. Toxicol. 51(3): 267-271.	10 g MT (= D1) = 30 mg alkaloids = 20.1 mg strychnine → 10 g D6 = 0.30 µg alkaloids = 0.201 µg strychnine	**D6**	Derivation of PDE strychnine: LOAEL rat 2.5 mg strychnine/kg/day divided by UF (F1-F5 = 10 x 10 x 10 x 1 x 10) = 0.00025 mg strychnine/kg/d = appr. 300 ng strychnine/kg/day rounded value of US EPA
Strychnos nux-vomica Ph. Eur.	Ph. Eur. 1.1.10 (Ph. Franç.)	Indole alkaloids: 0.15 - 0.30 % in MT, thereof 43 - 67 % strychnine → 10 g MT = 30 mg indole alkaloids = 20.1 mg strychnine	RfD	300 ng strychnine/kg/day → 0.9 µg strychnine/day (neonate)	US EPA Integrated Risk Information System: Strychnine. The RfD is calculated on the basis of the study from Seidl and Zbinden, 1982; Subchronic oral toxicity of strychnine in rats. Arch. Toxicol. 51(3): 267-271.	10 g MT = 30 mg alkaloids = 20.1 mg strychnine → 10 g D5 = 0.30 µg alkaloids = 0.201 µg strychnine	**D5**	Derivation of PDE strychnine: LOAEL rat 2.5 mg strychnine/kg/day divided by UF (F1-F5 = 10 x 10 x 10 x 1 x 10) = 0.00025 mg strychnine/kg/d = appr. 300 ng strychnine/kg/day rounded value of US EPA

1	2	3	4	5	6	7	8	9
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Veratrum album HAB	Ph. Eur. 1.1.8 (HAB 4a): MT = D1	Protoveratrine: 0.15 - 0.33 % in MT → 10 g MT = 33 mg protoveratrine	PDE	0.06 µg protoveratrine /kg/day → 0.18 µg protoveratrine /day (neonate)	Krayer O, Meilmann E, 1977, Veratrum Alkaloids with Antihypertensive Activity. In: Gross F (Hrsg.) Handbook of Experimental Pharmacology, Antihypertensive Agents, Springer-Verlag, Berlin Heidelberg, Bd. 39, S. 547–570	10 g MT (= D1) = 33 mg protoveratrine → 10 ml D7 = 0.03 µg protoveratrine	**D7**	Derivation of PDE protoveratrine: LOEL $_{hum}$ (lowest documented effect human dose i.v.) = 1.2 µg protoveratrine/kg divided by UF (F1-F5 = 1 x 10 x 1 x 1 x 10) = 12 ng protoveratrine/kg/day = parenteral PDE For oral intake and under consideration of 20 % resorption (as appropriately documented), the acceptable amount accounts for 60 ng protoveratrine/kg/day = 0.06 µg protoveratrine/kg/day (12 ng x 5).

1	2	3	4	5	6	7	8	9
Stock*/raw/starting material**	**Method of Preparation**	**Toxic component concentration**	**Basis for FSD**	**Acceptable amount**	**Reference(s)**	**Calculation method**	**FSD**	**Remarks**
Zincum isovalerianicum **$Zn(C_5H_9O_2)_2 \cdot 2H_2O$** HAB	Ph. Eur. 3.1.1 (HAB 5a) Ph. Eur. 4.1.2 (Ph. Franç.)	$Zn(C_5H_9O_2)_2 \cdot 2H_2O$: 0.93 - 1.08 % in D2 M_r = 303,7 Relative content zinc in stock = 21.7 % Relative content valeric acid in stock = 67,2 %	mean intakes per day adequate for the majority of infants of the first half-year of life (zinc) valeric acid: acceptable amount derived from allowed content in food for valerian root (3.6 g/day)	2 mg zinc/day 6.12 mg valeric acid/day	Zinc: Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union, EFSA Journal 2013;11(10):3408 Valeric acid: KB van 29/08/1997 betreffende de fabricage van en de handel in voedingsmiddelen die uit planten of uit plantenbereidingen samengesteld zijn of deze bevatten (http://www.gezondheid.belgie.be/eportal/foodsafety/19077598?ie2Term=planten&ie2section=9125)	10 g D2 = 108 mg raw material = 23.44 mg Zn and 72.58 mg valeric acid → 10 g D4 = 0.23 mg Zn and 0.73 mg valeric acid	**D4**	The acceptable amount of valeric acid is calculated on the basis of information given in the document "KB van 29/08/1997". On page 66 of the document, the intake of the dried root of Valeriana officinalis or equivalents to it via food is restricted to 3.6 g/day. According to the Ph. Eur. monograph Valerianae radix and the given content of valerianic acid in the monograph (0.17 %) a most conservative acceptable amount is calculated as 6.12 mg.

*As defined in the Ph. Eur.

**For information related to the identity, refer to "Guidance on module 3 of the homeopathic medicinal product dossier"