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## ICH guideline Q3D (R2) on elemental impurities Step 2b

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**  
**GUIDELINE FOR ELEMENTAL IMPURITIES**  
**Q3D(R2)**

Draft version

Endorsed on 25 September

*Currently under public consultation*

This document for public consultation is comprised of extracts of the Q3D(R2) Guideline with the revisions to the Q3D(R1) Guideline:

- Part 1 - Extract of Appendix 2: Correction of PDEs for Gold, Silver and Nickel
- Part 2 - Extract of Appendix 3: Correction of Gold monograph
- Part 3 - Extract of Appendix 3: Correction of Silver monograph
- Part 4 - New Appendix 5

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.*

**Q3D(R2)**  
**Document History**

Code	History	Date
Q3D(R2)	Endorsement by the Members of the ICH Assembly under <i>Step 2</i> and release for public consultation.	25 September 2020
Q3D(R1)	Revision of the Cadmium Inhalation PDE  Adoption by the Regulatory Members of the ICH Assembly under Step 4.	22 March 2019
Q3D(R1)	Revision of the Cadmium Inhalation PDE  Endorsement by the Members of the ICH Assembly under Step 2 and release for public consultation.	18 May 2018
Q3D	Corrigendum to correct: the modifying factor in the text of the safety assessment for Selenium (changed to 2 instead of 10 consistent with Section 3.1); and two references for consistency in the safety assessments for Barium (deleted reference) and Vanadium (revised reference).	16 December 2014
Q3D	Approval by the Steering Committee under Step 4 and recommendation for adoption to the ICH regulatory bodies.	12 November 2014
Q3D	Addition of line numbers to facilitate the provision of comments by stakeholders.	30 September 2013
Q3D	Post sign-off minor editorial corrections including: removal of references to Appendix 5 (pgs i & 13); deletion of redundant text (pg 4); change of Option 2 to Option 2a (pg 10); insertion of omitted text under Safety Limiting Toxicity (pg 35); removal of duplicated redundant text (pg 41); replacing references to “metals” in text and “metal” in Table A.4.7 title with “elementals” and “elements” (pg 73); and deletion of header Table A.4.10 (pg 75).	26 July 2013

Q3D	Post sign-off corrigendum in: <ul style="list-style-type: none"> <li>•Table 4.1 W and AI were removed from the list of included elemental impurities in Class 2B and 3 respectively.</li> <li>•Table A.2.1 the Class for Ni was changed to read 3 instead of 2.</li> </ul>	14 June 2013
Q3D	Approval by the Steering Committee under Step 2b and release for public consultation.	6 June 2013
Q3D	Approval by the Steering Committee under Step 2a.	6 June 2013

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## **Part 1 - Q3D Appendix 2 Extract – Correction of PDEs for Gold, Silver and Nickel**

Changes proposed to Appendix 2 are shown in track change, and are intended to be integrated into the Q3D(R2) Guideline

### 1 Appendix 2: Established PDEs for Elemental Impurities

#### 2 Table A.2.1: Permitted Daily Exposures for Elemental Impurities<sup>1</sup>

Element	Class <sup>2</sup>	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	<del>65</del>
Tl	2B	8	8	8
Au	2B	<del>100</del> <u>300</u>	<del>100</del> <u>300</u>	<del>13</del>
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	<del>10</del> <u>15</u>	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

3  
4 <sup>1</sup> PDEs reported in this table (µg/day) have been established on the basis of safety data described in the  
5 monographs in Appendix 3, and apply to new drug products. The PDEs in the monographs are not  
6 rounded. For practical purposes the PDEs in this table have been rounded to 1 or 2 significant figures.  
7 PDEs less than 10 have 1 significant figure and are rounded to the nearest unit. PDEs greater than 10 are  
8 rounded to 1 or 2 significant figures as appropriate. The principles applied to rounding in this table may  
9 be applied to PDEs derived for other routes of administration.

10 <sup>2</sup> Classification as defined in Section 4.

11

12

## **Part 1 - Q3D Appendix 2 Extract – Correction of PDEs for Gold, Silver and Nickel**

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13 **Table A.2.2: Permitted Concentrations of Elemental Impurities for Option 1**

14 The values presented in this table represent permitted concentrations in micrograms per gram for elemental  
 15 impurities in drug products, drug substances and excipients. These concentration limits are intended to be  
 16 used when Option 1 is selected to assess the elemental impurity content in drug products with daily doses  
 17 of not more than 10 grams per day. The numbers in this table are based on Table A.2.1.

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.3
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	<del>0.56</del>
Tl	2B	0.8	0.8	0.8
Au	2B	<del>3040</del>	<del>3040</del>	<del>0.34</del>
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	<del>1.5</del>	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

## Part 2 - Q3D Appendix 3 Extract – Correction of Gold Monograph

Changes proposed to Appendix 3 are shown in track change, and are intended to be integrated into the Q3D(R2) Guideline

### 19 GOLD

#### 20 Summary of PDE for Gold

Gold (Au)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	<del>134</del> 322	<del>134</del> 322	<del>1</del> 33.2

#### 21 Introduction

22 Gold (Au) exists in metallic form and in oxidation states of +1 to +5, the monovalent and trivalent forms  
23 being the most common. Elemental gold is poorly absorbed and consequently is not considered biologically  
24 active. Gold is being used on a carrier or in complexes like gold chloride and L-Au<sup>+</sup> (where L is a phosphane,  
25 phosphite, or an arsine; Telles, 1998), as catalysts in organic synthesis. The only source for gold in drug  
26 products comes from the use as catalyst. Au(1+) salts are used therapeutically.

#### 27 Safety Limiting Toxicity

28 Most knowledge of gold toxicity is based on therapeutic uses of gold. Currently available therapies are  
29 gold salts of monovalent Au(1+) with a sulfur ligand (Au-S), but metallic gold has also been studied. No  
30 toxicity was seen in 10 patients administered colloidal metallic gold (monoatomic gold) at 30 mg/day for  
31 one week followed by 60 mg/day the second week or the reverse schedule. The patients were continued on  
32 the trial for an additional 2 years at 30 mg/day. There was no evidence of hematologic, renal or hepatic  
33 cytotoxicity but some improvement in clinical symptoms of rheumatoid arthritis and in cytokine parameters  
34 were noted (Abraham and Himmel, 1997).

35 Long term animal and human data are available with gold compounds. Toxicities include renal lesions in  
36 rats administered gold compounds by injection (Payne and Saunders, 1978) and humans (Lee *et al*, 1965)  
37 and gastrointestinal toxicity in dogs (Payne and Arena, 1978). However, these studies have been performed  
38 with monovalent gold (Au(1+)) or forms of gold not present as pharmaceutical impurities and thus are not  
39 considered sufficiently relevant to derive a PDE for gold in pharmaceutical products.

40 There are no relevant toxicology studies in humans or animals by the oral route of a form of gold likely to  
41 be in a pharmaceutical product to set an oral PDE of gold. Au(3+) is thought to be the more toxic form and  
42 is used in catalysis, e.g., as gold trichloride. There is only limited data on Au(3+) complexes. In one study,  
43 the Au(3+) compound [Au(en)Cl<sub>2</sub>]Cl (dichloro(ethylenediamine-aurate<sup>3+</sup> ion) caused minimal histological  
44 changes in the kidney and liver of rats, and no renal tubular necrosis, at a dose of 32.2 mg/kg in ~~mice~~-rats  
45 administered the compound intra peritoneal for 14 days (Ahmed *et al*, 2012).

#### 46 PDE – Oral Exposure

47 The toxicologically significant endpoint for gold exposures is renal toxicity. The study in ~~mice~~-rats  
48 administered Au(3+) by the intra peritoneal route was considered acceptable in setting the oral PDE because  
49 the renal endpoint of toxicity is a sensitive endpoint of gold toxicity. Taking into account the modifying  
50 factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

51  
52 
$$\text{PDE} = 32.2 \text{ mg/kg} \times 50 \text{ kg} / \del{12.5} \times 10 \times 10 \times 1 \times 10 = \del{134}322 \mu\text{g/day}$$

53  
54 A factor of 10 for F5 was chosen because the LOAEL is used to establish the PDE and the toxicological  
55 assessment was not complete.

## Part 2 - Q3D Appendix 3 Extract – Correction of Gold Monograph

Changes proposed to Appendix 3 are shown in track change, and are intended to be integrated into the Q3D(R2) Guideline

### 56 PDE – Parenteral Exposure

57 In humans, 50 mg intramuscular injections of gold sodium thiomalate resulted in >95% bioavailability  
58 (Blocka *et al*, 1986). In rabbits, approximately 70% of the gold sodium thiomalate was absorbed after an  
59 intramuscular injection of 2/mg/kg (Melethil and Schoepp, 1987). Based on high bioavailability, and that  
60 a study by the intra peritoneal route was used to set the oral PDE, the parenteral PDE is equal to the oral  
61 PDE.

62  
63 PDE = ~~134~~322 µg/day

### 64 PDE – Inhalation Exposure

65 In the absence of relevant inhalation and parenteral data, including the potential local tissue toxicity of the  
66 effects of gold in lungs, the ~~inhalation parenteral~~-PDE was calculated by dividing the oral PDE by a  
67 modifying factor of 100 (as described in Section 3.1).

68  
69 PDE = ~~134~~322 µg/d / 100 = 3.22 ~~31.34~~ µg/day

### 70 REFERENCES

- 71 Abraham GE, Himmel PB. Management of rheumatoid arthritis: rationale for the use of colloidal metallic  
72 gold. J Nutr Environ Med 1997;7:295-305.
- 73 Ahmed A, Al Tamimi DM, Isab AA, Alkhawajah AMM, Shawarby MA. Histological changes in kidney  
74 and liver of rats due to gold (III) compound [Au(en)Cl<sub>2</sub>]Cl. PLoS ONE 2012;7(12):1-11.
- 75 Blocka KL, Paulus HE, Furst DE. Clinical pharmacokinetics of oral and injectable gold compounds. Clin  
76 Pharmacokinet 1986;11:133-43.
- 77 Lee JC, Dushkin M, Eyring EJ, Engleman EP, Hopper J Jr. Renal Lesions Associated with Gold Therapy:  
78 Light and Electron Microscopic Studies. Arthr Rheum 1965;8(5):1-13.
- 79 Melethil S, Schoepp D. Pharmacokinetics of gold sodium thiomalate in rabbits. Pharm Res 1987;4(4):332-  
80 6.
- 81 Payne BJ, Arena E. The subacute and chronic toxicity of SK&F 36914 and SK&F D-39162 in dogs. Vet  
82 Pathol 1978;15(suppl 5): 9-12.
- 83 Payne BJ, Saunders LZ. Heavy metal nephropathy of rodents. Vet Pathol 1978;15(suppl 5):51-87.
- 84 Telles JH, Brode S, Chabanas M. Cationic gold (I) complexes: highly efficient catalysts for the addition of  
85 alcohols to alkynes. Angew Chem Int Ed 1998;37:1415-18.



## Part 3 - Q3D Appendix 3 Extract – Correction of Silver Monograph

Changes proposed to Appendix 3 are shown in track change, and are intended to be integrated into the Q3D(R2) Guideline

### 86 SILVER

#### 87 Summary of PDE for Silver

Silver (Ag)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	167	<u>16.714</u>	7.0

#### 88 Introduction

89 Silver (Ag) is present in silver compounds primarily in the +1 oxidation state and less frequently in the +2  
90 oxidation state. Silver occurs naturally mainly in the form of very insoluble and immobile oxides, sulfides  
91 and some salts. The most important silver compounds in drinking-water are silver nitrate and silver chloride.  
92 Most foods contain traces of silver in the 10–100 µg/kg range. Silver is nutritionally not essential and no  
93 metabolic function is known. Silver is being used as a catalyst in the oxidation of ethylene to ethylene  
94 oxide. Silver-Cadmium alloy is used in selective hydrogenation of unsaturated carbonyl compounds. Silver  
95 oxide is used as a mild oxidizing agent in organic synthesis.

#### 96 Safety Limiting Toxicity

97 Silver is not mutagenic. Animal toxicity studies and human occupational studies have not provided  
98 sufficient evidence of carcinogenicity. Based on these data silver is not expected to be carcinogenic in  
99 humans (ATSDR, 1990).

100 Argyria appears to be the most sensitive clinical effect in response to human Ag intake. Silver acetate  
101 lozenges are used in smoking cessation (Hymowitz and Eckholdt, 1996). Argyria, a permanent bluish-gray  
102 discoloration of the skin, results from the deposition of Ag in the dermis combined with a silver-induced  
103 production of melanin. Inhalation of high levels of silver can result in lung and throat irritation and stomach  
104 pains (ATSDR, 1990).

#### 105 PDE – Oral Exposure

106 Silver nitrate was added at 0.015% to the drinking water of female mice (0.9 g/mouse; 32.14 mg/kg silver  
107 nitrate; 64% silver) for 125 days to examine neurobehavioral activity of the animals based on potential  
108 neurotoxicity of silver (Rungby and Danscher, 1984). Treated animals were hypoactive relative to controls;  
109 other clinical signs were not noted. In a separate study, silver was shown to be present in the brain after  
110 mice were injected with 1 mg/kg intra peritoneal silver lactate (Rungby and Danscher, 1983). The oral  
111 PDE is consistent with the reference dose of 5 µg/kg/day (US EPA, 2003). Taking into account the  
112 modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

$$113 \\ 114 \text{PDE} = 20 \text{ mg/kg} \times 50 \text{ kg} / 12 \times 10 \times 5 \times 1 \times 10 = 167 \text{ } \mu\text{g/day}$$

115  
116 A factor 10 was chosen for F5 because the LOAEL was used to set the PDE as few toxicological endpoints  
117 were examined.

#### 118 PDE – Parenteral Exposure

119  
120 ~~US EPA (2003) identified a LOAEL of 0.014 mg/kg Ag/day using long term (2 to 9 years) human~~  
121 ~~intravenous data based on argyria following colloidal and organic silver medication. Taking into account~~  
122 ~~the modifying factors (F1-F5 as discussed in Appendix 1), the parenteral PDE is calculated as below.~~

## Part 3 - Q3D Appendix 3 Extract – Correction of Silver Monograph

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$$PDE = 0.014 \text{ mg/kg/d} \times 50 \text{ kg} / 1 \times 10 \times 1 \times 1 \times 5 = 14 \text{ } \mu\text{g/day}$$

A factor of 5 was chosen for F5 as the finding of argyria was considered a LOEL because accumulation of silver in the skin is not considered adverse.

The safety review for silver identified one study in humans by the intravenous route published by Gaul and Staud in 1935. In this study silver arsphenamine was administered intravenously to 12 patients in 31-100 injections over 2 to 9.75 years. Based on cases presented in the study, the lowest level of silver resulting in argyria was 1 g metallic silver. Argyria was reported in other patients at higher cumulative doses of silver. Using this study, the US EPA (2003) identified this dose as a LOAEL. This study was considered inadequate to set a parenteral PDE as it involved few patients and the dosing was not adequately described. However, the study was useful in that it identified argyria as a result of cumulative dosing.

Silver is known to be absorbed across mucosal surfaces. Absorption of silver acetate occurred after ingestion of a dose of radiolabelled silver with approximately 21% of the dose being retained at 1 week (ATSDR, 1990). In a review of the oral toxicity of silver, Hadrup and Lam (2014) report that absorption of a radionuclide of silver (as silver nitrate) was between 0.4 to 18%, depending upon the species, with humans at 18%. On the basis of an oral bioavailability between 1% and 50% for silver, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1). The recommended PDE for silver for parenteral exposure is:

$$PDE = 167 \text{ } \mu\text{g/d} / 10 = 16.7 \text{ } \mu\text{g/day}$$

### PDE – Inhalation Exposure

Lung and throat irritation and stomach pains were the principal effects in humans after inhalation of high Ag levels. Using the Threshold Limit Value (TLV) of 0.01 mg/m<sup>3</sup> for silver metal and soluble compounds (US DoL, 2013), and taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{0.01 \text{ mg/m}^3 \times 8 \text{ hr/d} \times 5 \text{ d/wk}}{24 \text{ hr/d} \times 7 \text{ d/wk}} = \frac{0.0024 \text{ mg/m}^3}{1000 \text{ L/m}^3} = 0.00000238 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.0000024 \text{ mg/L} \times 28800 \text{ L/d}}{50 \text{ kg}} = 0.0014 \text{ mg/kg/day}$$

$$PDE = 0.0014 \text{ mg/kg} \times 50 \text{ kg} / 1 \times 10 \times 1 \times 1 \times 1 = 0.007 \text{ mg/d} = 7.0 \text{ } \mu\text{g/day}$$

### REFERENCES

ATSDR. Toxicological Profile for Silver. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 1990.

Gaul LE, Staud AH. Clinical spectroscopy. Seventy cases of generalized argyrosis following organic and colloidal Ag medication. JAMA. 1935, 104:1387–1390.

### Part 3 - Q3D Appendix 3 Extract – Correction of Silver Monograph

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- 166 Hadrup N, Lam HR. Oral toxicity of silver ions, silver nanoparticles and colloidal silver - A review. Regul  
167 Toxicol Pharmacol. 2014 68(1):1-7.
- 168 Hymowitz N, Eckholt H. Effects of a 2.5-mg silver acetate lozenge on initial and long-term smoking  
169 cessation. *Prev Med* 1996;25:537-46.
- 170 Rungby J, Danscher G. Hypoactivity in silver exposed mice. *Acta Pharmacol Toxicol* 1984;55:398-401.
- 171 Rungby J, Danscher G. Localization of exogenous silver in brain and spinal cord of silver exposed rats.  
172 *Acta Neuropathol* 1983;60(1-2):92-8.
- 173 US DoL (OHSA). 29 CFR 1910.1000 Table Z-1. Limits for air contaminants. U.S. Department of Labor.  
174 2013.
- 175 US EPA. Silver (CASRN 7440-22-4). Integrated Risk Information System (IRIS). 2003.

## Part 4 - Q3D Appendix 5

The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline

### Appendix 5: Limits for Elemental Impurities by the Cutaneous and Transcutaneous Route

178

179

#### Table of Contents

180	<b>1</b>	<b>BACKGROUND</b> .....	<b>8</b>
181	<b>2</b>	<b>SCOPE</b> .....	<b>9</b>
182	<b>3</b>	<b>PRINCIPLES OF SAFETY ASSESSMENT FOR CUTANEOUS PRODUCTS</b> .....	<b>10</b>
183	3.1	Transcutaneous absorption of Elemental Impurities (EI) .....	10
184	3.2	PDE for drug products directly applied to the dermis.....	11
185	<b>4</b>	<b>ESTABLISHING THE CUTANEOUS PERMITTED DAILY EXPOSURE (PDE)</b> .....	<b>11</b>
186	4.1	Establishing the cutaneous modifying factor (CMF).....	12
187	4.2	Cutaneous PDE .....	12
188	4.2.1	Derivation of PDE for EI, other than thallium (Tl) and arsenic (As).....	12
189	4.2.2	Derivation of PDE for arsenic.....	13
190	4.2.3	Derivation of PDE for thallium .....	13
191	<b>5</b>	<b>CUTANEOUS CONCENTRATION LIMITS FOR NI AND CO</b> .....	<b>13</b>
192	<b>6</b>	<b>PRODUCT RISK ASSESSMENT</b> .....	<b>14</b>
193	<b>7</b>	<b>CUTANEOUS PDE VALUES</b> .....	<b>16</b>
194	<b>8</b>	<b>REFERENCES</b> .....	<b>17</b>

195

#### 1 BACKGROUND

197

198 In December 2014, ICH approved the ICH Q3D Guideline for Elemental Impurities developed by  
199 the Expert Working Group. The Guideline provided Permitted Daily Exposures (PDEs) for 24  
200 elemental impurities (EI) for the oral, parenteral, and inhalation routes of administration. In section  
201 3.2 of the guideline, principles for establishing PDEs for other routes of administration are  
202 described. During the course of the development of Q3D, interest was expressed in developing  
203 PDEs for the cutaneous and transcutaneous route, as these products remain the most significant  
204 area where PDEs for EI have not been formally established.

205

206 In establishing cutaneous and transcutaneous limits, the role of skin is paramount. The skin is an  
207 environmental barrier and a complex organ that has many functions, including limiting the  
208 penetration of exogenous materials, metabolism, prevention of water loss, temperature regulation,  
209 and as an immune organ (Monteiro-Riviere and Filon, 2017). The skin is composed of both an

## Part 4 - Q3D Appendix 5

The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline

210 outer epidermis and an inner dermis, each composed of multiple cellular layers. Dermal (or  
211 transcutaneous) absorption, i.e., the transport of a chemical from the outer surface of the skin into  
212 systemic circulation, is dependent upon the properties of the skin, the anatomical site, the nature  
213 of the chemical applied and the characteristics of the application.

214 The primary barrier to absorption is the outermost layer of the epidermis (i.e., the stratum corneum)  
215 which typically consists of 15-20 layers of non-viable cells. The stratum corneum (horny layer)  
216 serves as a highly effective barrier, especially to hydrophobic compounds and charged molecules,  
217 such as metal ions. For this reason, transcutaneous delivery into the systemic circulation of  
218 materials including any active pharmaceutical ingredient (API) typically requires physical and  
219 chemical agents (e.g., penetration enhancers) to assist in the transcutaneous absorption of the API.  
220

221 In respect to these “penetration enhancers,” it is noteworthy that agents that enhance penetration  
222 of an API are usually not applicable for EI due to fundamental differences in physico-chemical  
223 properties. Limited research has been conducted to evaluate the systemic absorption of EIs applied  
224 to the skin. The skin may respond to exposure in various ways. For example, approximately half  
225 of mercury vapor taken up by the skin (1 - 4% of the dose) was shed by desquamation of epidermal  
226 cells for several weeks after exposure, while the remainder in the skin was slowly released into  
227 general circulation (Hursh et al., 1989). Hostýnek et al. (1993) describes that silver (Ag) is  
228 preferentially accumulated in the skin and is not liberated. Available data indicates that gold (Au)  
229 is not readily absorbed through skin due to inertness and lack of ionization by bodily fluids  
230 (Lansdown, 2012). Gold, in salt form, has been shown to bind readily to sulfhydryl groups of  
231 epidermal keratin and remain in the skin (Lansdown, 2012). Metal binding proteins are present in  
232 some fetal and adult skin (e.g., basal keratinocytes of epidermis and outer hair root sheath) but not  
233 in other cell types (e.g., exocrine portion of the eccrine glands), indicating the skin has the potential  
234 for binding and metabolism of metals (van den Oord and De Ley, 1994)  
235

236 Together these properties of the skin layers represent a significant barrier to systemic exposure as  
237 illustrated by quantitative absorption data reviewed by Hostýnek et al. (1993). This systemic  
238 exposure is reported to be < 1% absorption for most of the evaluated EI in scope of this guideline.  
239 Transcutaneous absorption of EI is discussed in more detail in section 3.  
240

241 Elements evaluated in this guideline were assessed by reviewing publicly available data contained  
242 in scientific journals, government research reports and studies, and regulatory authority research  
243 and assessment reports. In general, studies in the scientific literature simply report disappearance  
244 of EI from the cutaneous layer rather than transcutaneous absorption. Quantitative data are  
245 generally lacking for most EI and the associated counterion (Hostýnek, 2003). Furthermore, there  
246 are no suitable standards for occupational exposure for the dermal route for risk assessment.  
247 Consequently, a generic approach was adopted to establish limits as opposed to an element-by-  
248 element basis.  
249

## 250 **2 SCOPE**

251  
252 This Appendix to Q3D applies to cutaneous and transcutaneous drug products (referred to as  
253 “cutaneous products” throughout this Appendix) whether intended for local or systemic effect.

## Part 4 - Q3D Appendix 5

The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline

254 This Appendix does not apply to drug products intended for mucosal administration (oral, nasal,  
255 vaginal), topical ophthalmic, rectal, or subcutaneous and subdermal routes of administration.

256

### 257 **3 PRINCIPLES OF SAFETY ASSESSMENT FOR CUTANEOUS** 258 **PRODUCTS**

259

260 The literature review focuses on the forms likely to be present in pharmaceutical products (see  
261 main guideline) and therefore the assessment relied on evaluating the available data for inorganic  
262 forms of the EI and ranking the relevance of the data in the following order: human *in vivo* data;  
263 animal *in vivo* data; *in vitro* data.

264 Local and systemic toxicities were considered. In general, there is no indication for local toxicity  
265 on the skin, with the exception of sensitization. Review of systemic toxicity by the dermal route,  
266 shows significant systemic toxicity for thallium. Since there is limited information available on  
267 transcutaneous absorption of the elements addressed in this Addendum and it is not possible to  
268 address this percent absorption on an element-by-element basis and to allow conversion of an  
269 existing PDE to the dermal route in order to support an element-by-element approach. Therefore  
270 a generic approach has been developed based on a systematic adjustment of the parenteral PDE,  
271 which assumed 100% bioavailability, to derive a cutaneous PDE by using a Cutaneous Modifying  
272 Factor (CMF) (see section 4). The cutaneous PDE has been derived for daily, chronic application  
273 to the skin.

274

#### 275 **3.1 Transcutaneous Absorption of Elemental Impurities (EI)**

276 The extent of absorption into the systemic circulation (systemic absorption) is considered an  
277 important component to the safety assessment of the elements. Review of studies of skin  
278 penetration, absorption, systemic bioavailability and toxicity of the elements shows a lack of data  
279 for many elements. For those elements that have been studied for transcutaneous absorption and/or  
280 toxicity, the available data are rarely suitable for proper quantitative analysis and the diverse  
281 experimental designs preclude inter-study or inter-element comparability (Hostynek, 2003). The  
282 available data indicate that EIs are generally poorly absorbed through intact skin even in the  
283 presence of enhancers. For example, absorption of Pb from lead oxide under occlusion in rats was  
284 less than 0.005%, as measured by urinary Pb for 12 days following exposure. Penetration of lead  
285 oxide was not detectable in an *in vitro* system with human skin (ATSDR, 2019).

286 There are numerous factors that may influence transcutaneous absorption and systemic  
287 bioavailability after cutaneous administration of a substance. These factors may be categorized as:

- 288 • compound-related factors (e.g., physical state, ionization, solubility, binding properties,  
289 reactivity, and the counterion of the EI), and/or

## Part 4 - Q3D Appendix 5

The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline

- application-related factors (e.g., concentration and total dose applied, duration of application/exposure, cleaning between applications, surface area, co-applied materials/excipients and occlusion status),
- subject-related factors (e.g., comparative species differences, location on the body, hydration of the skin/age, temperature).

Transcutaneous penetration through the skin is element and chemical species-specific and each element would need to be experimentally assessed under different conditions to develop an effective model. Due to this complexity, it is not feasible to address every possible scenario for each EI in each drug product.

Given the limited amount of data on transcutaneous absorption and toxicity by the cutaneous route of administration that has been generated in well-designed studies, the available data were used to develop a generic, conservative approach. The cutaneous PDE is derived from the previously established element-specific parenteral PDEs for which adequate toxicity data are available. To address the presumed low but unquantified transcutaneous absorption, and in consideration of all the potential factors that can influence this absorption, a 10-fold factor will be applied to the parenteral PDE for most EIs. The derivation and application of the factor of 10 is described in more detail in section 4 below.

307

### 3.2 PDE for Drug Products Directly Applied to the Dermis

A compromised basal cell layer could facilitate direct entry of EIs into the dermis and its associated blood vessels (potentially increasing systemic absorption). Therefore, the generic PDE for the cutaneous route described in this Addendum should not be applied to drug products intended to treat skin with substantial disruption of the basal cell layer of the epidermis. For indications in which drug is intentionally brought into contact with the dermis (e.g. skin ulcers, second- and third-degree burns, pemphigus, epidermolysis bullosa) it is recommended to develop a case-specific justification based on principles outlined in ICH Q3D section 3.3. The parenteral PDE is generally an appropriate starting point for these drug products.

Small cuts, needle pricks, skin abrasions and other quick healing daily skin injuries are not associated with substantial basal cell layer disruption of the epidermis as defined above. The total amount of drug product which can potentially come into contact with the dermis is therefore considered negligible. Therefore, cutaneous PDEs will apply to products intended to treat these skin abrasions or other quick healing acute injuries.

322

## 4 ESTABLISHING THE CUTANEOUS PERMITTED DAILY EXPOSURE (PDE)

323

324

325

326

327

The cutaneous PDE for all relevant EIs is calculated by applying a cutaneous modifying factor (CMF) to the parenteral PDE for each EI.

## Part 4 - Q3D Appendix 5

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328

### 329 4.1 Establishing the Cutaneous Modifying Factor (CMF)

330 The limited available data suggest that transcutaneous absorption of most EI, when studied in intact  
331 skin, is less than 1% as described previously (Section 1 and 3). As described in section 3.1, there  
332 are multiple factors that can influence this absorption. In lieu of accounting for such factors  
333 individually, and in consideration of the relative lack of reliable quantitative transcutaneous  
334 absorption data, an approach has been adopted for the derivation of cutaneous PDEs, which is  
335 considered protective against potential systemic toxicities. To account for these uncertainties, a  
336 CMF is generated using the approach outlined below.

337

338 1. For EIs other than arsenic (As) and thallium (Tl), a maximum Cutaneous Bioavailability  
339 (CBA) of 1% is used.

340

341 2. To account for the various factors that can enhance CBA, a factor of 10 is applied to  
342 increase the CBA (adjusted CBA).

343

344 3. To calculate the CMF, the parenteral BA (100%) is divided by the adjusted CBA

345

### 346 4.2 Cutaneous PDE

347 The Cutaneous PDE is calculated as

$$348 \text{ Cutaneous PDE} = \text{Parenteral PDE} \times \text{CMF}$$

349 Parenteral PDE calculations already include safety factors F1-F5 or are derived from Oral PDE,  
350 which also include safety factors (see Appendix 1of ICH Q3D) to account for variability and  
351 extrapolation. Therefore, no further adjustments are necessary for the cutaneous PDE.

352 The derived cutaneous PDEs are listed in Table 1.

#### 353 4.2.1 Derivation of PDE for EI, other than Thallium (Tl) and Arsenic (As)

354 For EI with low CBA ( $\leq 1\%$ ), a CMF of 10 is applied.

355

356 For EI with  $\leq 1\%$  CBA, the adjusted CBA is  $1\% \times 10 = 10\%$

357 Divide the parenteral BA by the adjusted CBA to derive the CMF

$$358 \frac{100\%}{10\%} = 10$$

359

360 The cutaneous PDE is derived as:

$$361 \text{ Cutaneous PDE} = \text{Parenteral PDE} \times \text{CMF}$$

$$362 \text{ Cutaneous PDE} = \text{Parenteral PDE} \times 10$$

363

364 See Table 1 for cutaneous PDEs for individual EI.

365



## Part 4 - Q3D Appendix 5

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### 366 4.2.2 Derivation of PDE for Arsenic

367 For inorganic arsenic, the available data indicate that the transcutaneous absorption is greater than  
368 that observed for most other EI (approximately 5%) (ATSDR, 2016). Based on this, the CMF for  
369 arsenic is 2, as shown in the calculation below

370

371 Derive the adjusted CBA:  $5\% \times 10 = 50\%$

372 Divide parenteral BA by the adjusted CBA to derive the CMF

373  $100\%/50\% = 2$

374

375 The cutaneous PDE is derived as:

376 Cutaneous PDE = Parenteral PDE x CMF

377 Cutaneous PDE =  $15 \mu\text{g}/\text{day} \times 2 = 30 \mu\text{g}/\text{day}$

378

### 379 4.2.3 Derivation of PDE for Thallium

380 Thallium is highly absorbed through the skin. Since quantitative data are not available, it is  
381 assumed to be effectively equivalent to parenteral levels. The adjusted PDE equals the parenteral  
382 PDE, a CMF of 1 is used.

383

384 The cutaneous PDE is derived as:

385 Parenteral PDE =  $8 \mu\text{g}/\text{day}$

386 Cutaneous PDE =  $8 \mu\text{g}/\text{day} \times 1 = 8 \mu\text{g}/\text{day}$

387

388

## 389 5 CUTANEOUS CONCENTRATION LIMITS FOR NI AND CO

390 The concentrations of EI generally present in cutaneous products as impurities are not considered  
391 sufficient to induce sensitization. However, a concentration limit in addition to the PDE is  
392 warranted for Nickel (Ni) and Cobalt (Co) to reduce the likelihood of eliciting skin reactions in  
393 already sensitized individuals. This concentration limit is referred to as the cutaneous and  
394 transcutaneous concentration limit (CTCL). For other EI such as Chromium (Cr), the threshold to  
395 elicit a sensitizing response is either approximately equal to the cutaneous PDE (Cr) or much  
396 greater than the cutaneous PDE and therefore additional controls are not necessary (Nethercott et  
397 al., 1994).

398

399 The dermal concentration limit of  $0.5 \mu\text{g}/\text{cm}^2/\text{week}$  for Ni was originally established by Menné et  
400 al., (1987) as a detection limit in the dimethylglyoxime (DMG) test. The use of Ni in consumer  
401 products (e.g., jewelry) intended for direct and prolonged skin contact was regulated by this limit  
402 under the EU countries Ni regulations and under the EU Nickel Directive (currently, REACH,  
403 Entry 27, Annex XVII). After implementation of the directive, the prevalence of Ni allergy  
404 decreased significantly (Thyssen et al., 2011; Ahlström et al., 2019). This limit is applied to set a  
405 cutaneous concentration of Ni in drug products. Based on application of 0.5 g dose of drug product  
406 to a skin surface area of  $250 \text{ cm}^2$  (Long and Finlay, 1991), a CTCL of  $35 \mu\text{g}/\text{g}/\text{day}$  drug product is

## Part 4 - Q3D Appendix 5

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407 derived, as below. A recently derived limit to minimize elicitation of allergies to Co shows a  
408 similar limit of 31-259 ppm (Fischer et al., 2015).

409  $0.5 \mu\text{g}/\text{cm}^2/\text{week} = 0.07 \mu\text{g}/\text{cm}^2/\text{day}$

410  $0.07 \mu\text{g}/\text{cm}^2/\text{day} \times 250 \text{ cm}^2 = 17.5 \mu\text{g}/\text{day}$

411  $17.5 \mu\text{g}/\text{day}/0.5 \text{ g} = 35 \mu\text{g}/\text{g}/\text{day}$

412

413

### 414 **6 PRODUCT RISK ASSESSMENT**

415

416 Product assessments for cutaneous drug products should be prepared following the guidance  
417 provided in ICH Q3D Section 5. The considerations of potential sources of EI, calculation options  
418 and considerations for additional controls are the same for products for the cutaneous route of  
419 administration as for products for the oral, parenteral and inhalation routes of administration.

420

421 For Ni and Co, in addition to considering the EI levels in the drug product relative to the PDE, the  
422 concentration of this EI ( $\mu\text{g}/\text{g}$ ) in the drug product should be assessed relative to the CTCL  
423 identified in Table 1. The product risk assessment should therefore confirm that the total Ni and  
424 Co level ( $\mu\text{g}/\text{day}$ ) is at or below the PDE and that their respective concentrations in the drug  
425 product does not exceed the CTCL shown in Table 1.

426 As described in ICH Q3D Section 5.2, the drug product risk assessment is summarized by  
427 reviewing relevant product or component specific data combined with information and knowledge  
428 gained across products or processes to identify the significant probable EI that may be observed in  
429 the drug product.

430 The summary should consider the significance of the observed or predicted level of the EI relative  
431 to the corresponding PDE and in the case of Ni and Co, the Ni- and Co-CTCL. As a measure of  
432 the significance of the observed EI level, a control threshold is defined as a level that is 30% of  
433 the established PDE (and CTCL for Ni and Co) in the drug product. The control threshold may be  
434 used to determine if additional controls may be required. If the total EI level - observed or  
435 predicted EI level ( $\mu\text{g}/\text{day}$ ) or CTCL ( $\mu\text{g}/\text{g}$ )- from all sources in the drug product is consistently  
436 less than 30% of the established PDE, then additional controls are not required, provided the  
437 applicant has appropriately assessed the data and demonstrated adequate controls on elemental  
438 impurities.

439

440 Since the maximum total daily dose for cutaneous products is not always so clearly stated, a  
441 prerequisite for the product risk assessment is a justified estimation of a worst-case exposure that  
442 can form the basis for the assessment. (SCCP, 2006; Long, 1991, Api et al., 2008)

443 Dermal products differ from oral, parenteral or inhalation products in that they may be removed  
444 or rinsed from the area of application. In evaluating the potential EI to which the patient may be  
445 exposed, it may be important to evaluate the retention time of the drug product during typical

## **Part 4 - Q3D Appendix 5**

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446 conditions of use. For example, certain products such as shampoos have a short application  
447 duration time. Thus, the risk assessment may propose an adjustment by use of a retention factor  
448 (see Module 1 of the ICH Q3D training package for more information on retention time;  
449 <https://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>). If the PDE is  
450 adjusted in this manner, the new level proposed should be referred to as an Acceptable Level and  
451 is subject to consideration by the relevant authorities on a case-by-case basis.  
452

## Part 4 - Q3D Appendix 5

The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline

### 453 7 CUTANEOUS PDE VALUES

454 The calculated PDE for the cutaneous and transcutaneous route are listed in Table 1. To be  
455 compliant with Q3D, for sensitizing EI (Ni, Co), a second limit- the CTCL ( $\mu\text{g/g/day}$ )- will also  
456 need to be met.

457 There are insufficient data to set PDEs by any route of administration for iridium, osmium,  
458 rhodium, and ruthenium. For these elements, the palladium PDE for the relevant route will apply.

459 Table 2 provides example concentrations for a drug product with a daily dose of 10 g.

460 **Table 1: Cutaneous products – PDE, CTCL and elements to be included in risk assessment**

Element	Class	From ICH Q3D(R1) for comparison			Cutaneous products		
		PDE ( $\mu\text{g/day}$ )			PDE ( $\mu\text{g/day}$ )	CTCL ( $\mu\text{g/g}$ ) for sensitizers	Include in Risk Assessment if not intentionally added <sup>1,2,3</sup>
		Oral	Parenteral	Inhalation			
Cd	1	5	2	3	20	-	yes
Pb	1	5	5	5	50	-	yes
As	1	15	15	2	30	-	yes
Hg	1	30	3	1	30	-	yes
Co	2A	50	5	3	50	35	yes
V	2A	100	10	1	100	-	yes
Ni	2A	200	20	6	200	35	yes
Tl	2B	8	8	8	8	-	no
Au	2B	300	300	3	3000	-	no
Pd <sup>4</sup>	2B	100	10	1	100	-	no
Se	2B	150	80	130	800	-	no
Ag	2B	150	15	7	150	-	no
Pt	2B	100	10	1	100	-	no
Li	3	550	250	25	2500	-	no
Sb	3	1200	90	20	900	-	no
Ba	3	1400	700	300	7000	-	no
Mo	3	3000	1500	10	15000	-	no
Cu	3	3000	300	30	3000	-	no
Sn	3	6000	600	60	6000	-	no
Cr	3	11000	1100	3	11000	-	no

461 <sup>1</sup> Intentionally added elements should always be included in the Risk Assessment.

462 <sup>2</sup> Class 2B elements were excluded from the assessment of oral, parenteral and inhalation products due to the low  
463 likelihood that they would be present if not intentionally added (see section 4 of ICH Q3D).

464 <sup>3</sup> Class 3 elements with a cutaneous PDE above 500  $\mu\text{g/day}$  do not have to be included in the risk assessment unless  
465 intentionally added (see section 4 of ICH Q3D)

466 <sup>4</sup> Pd PDE will apply to iridium, osmium, rhodium, and ruthenium.

467

## Part 4 - Q3D Appendix 5

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468 **Table 2: Cutaneous PDE and Concentration Limits for a 10 g Dose**

Element	Class	Cutaneous PDE (µg/day)	Cutaneous conc <sup>1</sup> for a 10 g daily dose (µg/g)	CTCL (µg/g) for sensitizers
Cd	1	20	2	-
Pb	1	50	5	-
As	1	30	3	-
Hg	1	30	3	-
Co	2A	50	5 <sup>b</sup>	35
V	2A	100	10	-
Ni	2A	200	20 <sup>2</sup>	35
Tl	2B	8	0.8	-
Au	2B	3000	300	-
Pd <sup>3</sup>	2B	100	10	-
Se	2B	800	80	-
Ag	2B	150	15	-
Pt	2B	100	10	-
Li	3	2500	250	-
Sb	3	900	90	-
Ba	3	7000	700	-
Mo	3	15000	1500	-
Cu	3	3000	300	-
Sn	3	6000	600	-
Cr	3	11000	1100	-

469

470 <sup>1</sup> PDE expressed in concentration terms, calculated using a 10 g daily dose;

471 <sup>2</sup> For elements with a cutaneous PDE and a CTCL, both limits need to be met. In case, the results are conflicting the  
472 lowest limit needs to be applied. As example: for Co: based on a 10 g dose, the calculated cutaneous concentration is  
473 5 µg/g is; a 1 g dose would permit a daily concentration of 50 µg/g, exceeding the CTCL of 35 µg/g. In this  
474 situation, the CTCL limit should be used.

475 <sup>3</sup> Pd PDE will apply to iridium, osmium, rhodium, and ruthenium.

476

## 477 **8 REFERENCES**

478

479 Ahlström MG, Thyssen JP, Wennervaldt M, Menné T, Johansen JD. Nickel allergy and allergic  
480 contact dermatitis: A clinical review of immunology, epidemiology, exposure and treatment.  
481 Contact Dermatitis 2019; 1-15.

482

483 Api AA, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick ZF, Griem P, McNamee PM,  
484 Ryan CA, Safford R. Dermal sensitization quantitative risk assessment (QRA) for fragrance  
485 ingredients. Reg Toxicol Pharmacol 52 (1) 2008, 3-23.

## Part 4 - Q3D Appendix 5

The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline

486  
487 ATSDR. Toxicological profile for lead. Agency for Toxic Substances and Disease Registry, Public  
488 Health Service, U.S. Department of Health and Human Services, Atlanta GA. 2019.

489 ATSDR. Addendum to the toxicological profile for arsenic Agency for Toxic Substances and  
490 Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta  
491 GA. 2016.

492  
493 Fischer LA, Johansen JD, Voelund A, Lidén C, et al. Elicitation threshold of cobalt chloride:  
494 analysis of patch test dose-response studies. *Contact Dermatitis* 2015; 74: 105-109.

495  
496 Hostýnek JJ, Hinz RS, Lorence CR, Price M, Guy RH. Metals and the skin. *Critical Reviews in*  
497 *Toxicology* 1993; 23(2): 171-235.

498  
499 Hostynek JJ. Factors determining percutaneous metal absorption. *Food Chem Toxicol* 2003; 41  
500 (3): 327–345.

501  
502 Hursh JB, Clarkson TW, Miles EF, Goldsmith LA. Percutaneous absorption of mercury vapor by  
503 man. *Arch Environ Health* 1989; 44(2): 120-127.

504 Lansdown ABG. Silver and Gold. In *Patty's Toxicology 6<sup>th</sup> Edition*. Ed Bingham E., Cofrssen B;  
505 John Wiley & Sons 2012; pp 75-112

506  
507 Long CC, and Finlay AY. The Finger-Tip Unit-a New Practical Measure. *Clinical and*  
508 *experimental dermatology*. 1991; 16.6: 444–447.

509  
510 Menné T, Brandup F, Thestrup-Pedersen K et al. Patch test reactivity to nickel alloys. *Contact*  
511 *Dermatitis* 1987; 16: 255-259.

512  
513 Monteiro-Riviere NA, Filon, FL. Skin. In B Badeel, A Pietroiusti and Anna A. Shvedova *Adverse*  
514 *Effects of Engineered Nanomaterials. Exposure, Toxicology and Impact on human Health 2<sup>nd</sup>*  
515 *Edition* 2017: 357-380 Elsevier

516  
517 Nethercott J, Paustenbach D, Adams R, Fowler J, et al. A study of chromium induced allergic  
518 contact with 54 volunteers: implications for environmental risk assessment. *Occup Environ Med*  
519 1994; 51: 371-380.

520  
521 SCCP's (European Commission Scientific Committee on Consumer Products) *Notes of Guidance*  
522 *for the Testing of Cosmetic Ingredients and Their Safety Evaluation*, sixth revision, 2006.  
523 [http://ec.europa.eu/health/ph\\_risk/committees/04\\_sccp/docs/sccp\\_o\\_03j.pdf](http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_03j.pdf) .

524

## **Part 4 - Q3D Appendix 5**

**The new proposed Appendix 5 is intended to be integrated into the Q3D(R2) Guideline**

- 525 Thyssen JP, Uter W, McFadden J, Menné T, Spiewalk R, Vigan M, Gimenez-Arnau A, Lidén C.  
526 The EU Nickel Directive revisited—future steps towards better protection against nickel allergy.  
527 Contact Dermatitis. 2011; 64(3): 121-125.  
528  
529 Van den Oord JJ and De Ley M. Distribution of metallothionein in normal and pathological human  
530 skin. Arch Dermatol Res 1994; 286: 62-8.