UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE

PERICOLO, RISCHIO, FATTORI CHIAVE NELLE VALUTAZIONE DI SICUREZZA DEI PRODOTTI COSMETICI: CASE STUDIES

CORRADO LODOVICO GALLI

CORSO TEORICO-PRATICO DI VALUTAZIONE DELLA SICUREZZA DEI COSMETICI

ALLA LUCE DEL REGOLAMENTO 1223/2009

LUNEDI 15 APRILE - VENERDI 19 APRILE 2013

CENTRO DIDATTICO UNIVERSITA DEGLI STUDI DI MILANO VIA CELORIA, 22 MILANO

TTC APPLICATIONS

- **Migrant** substances from packaging materials (USFDA-TOR- 1993)
- **Flavourings** substances in food (WHO-JECFA 1993,1995,1999….)
- Endorsed for the risk assessment of chemicals (WHO-IPCS 1998)
- Non relevant **plant protection product metabolites** in ground water (EC-2002)
- **Genotoxic impurities** in pharmaceutical preparations (EMA 2003,2004)
- **Flavourings** substances in food (EFSA 2004)
- **Genotoxic constituents** in herbal preparations (EMA 2006)
- Suggested for **REACH** (**R**egistr, **E**valuat, **A**uthoriz and restrict of **Ch**emical substances) (ECHA 2008)

- Suggested for application to **aquatic environmental** exposure (2005)
- **SUGGESTED FOR APPLICATION TO THE COSMETIC INGREDIENTS AND THEIR IMPURITIES (2007)**
- Suggested for **prenatal developmental** toxicity (2010)
- Suggested for **mixture of substances** potentially detectable in surface water (2011)
- Suggested for risk prioritization of **trace chemicals in food**. *(2011)*

APPLICATION OF THE TTC TO COSMETIC INGREDIENTS

Michael Gibney, Dublin, EIR

Corrado Galli, Milano, I

Andy Renwick, Southampton, UK

Richard Guy, Bath, UK

Robert Kroes, Utrecht, NL

Helmut Greim, Munich, D

Victor Feron, Zeist, NL

Jean-Claude Lhuguneot, Dijon, F

J.M. van de Sandt, Zeist, NL

Kroes et al. FCT 2007

APPLICATION OF THE KROES ET AL TTC DECISION TREE TO COSMETIC INGREDIENTS AND THEIR IMPURITIES

- **TTC values**

  Do the chemicals used in cosmetics resemble those in the database used to derive the TTC values?

  Does the route of exposure alter the potential for metabolic detoxication/bioactivation and validity of the TTC/NOAELs?

- **Exposure**

  Can the extent of systemic uptake be modelled using the compound's physicochemical properties? Can different exposure scenarios be allowed for by realistic uptake adjustment factors?

Kroes et al. FCT 2007

SIMILARITY TO COMPOUNDS IN MUNRO ET AL. (1996) DATABASE

Fragrance ingredients	YES
Dyes and colourants	YES
Food-type components	YES
Low molecular weight organic compounds with various uses	YES
Normal organic constituents of the human body	YES
Pharmaceutical-type compounds	YES
Surfactants, emollients, humectants and emulsifying agents	YES
Plant and animal extracts	NO
Polymeric compounds (YES-monomers)	NO
Inorganic salts of various metals	NO

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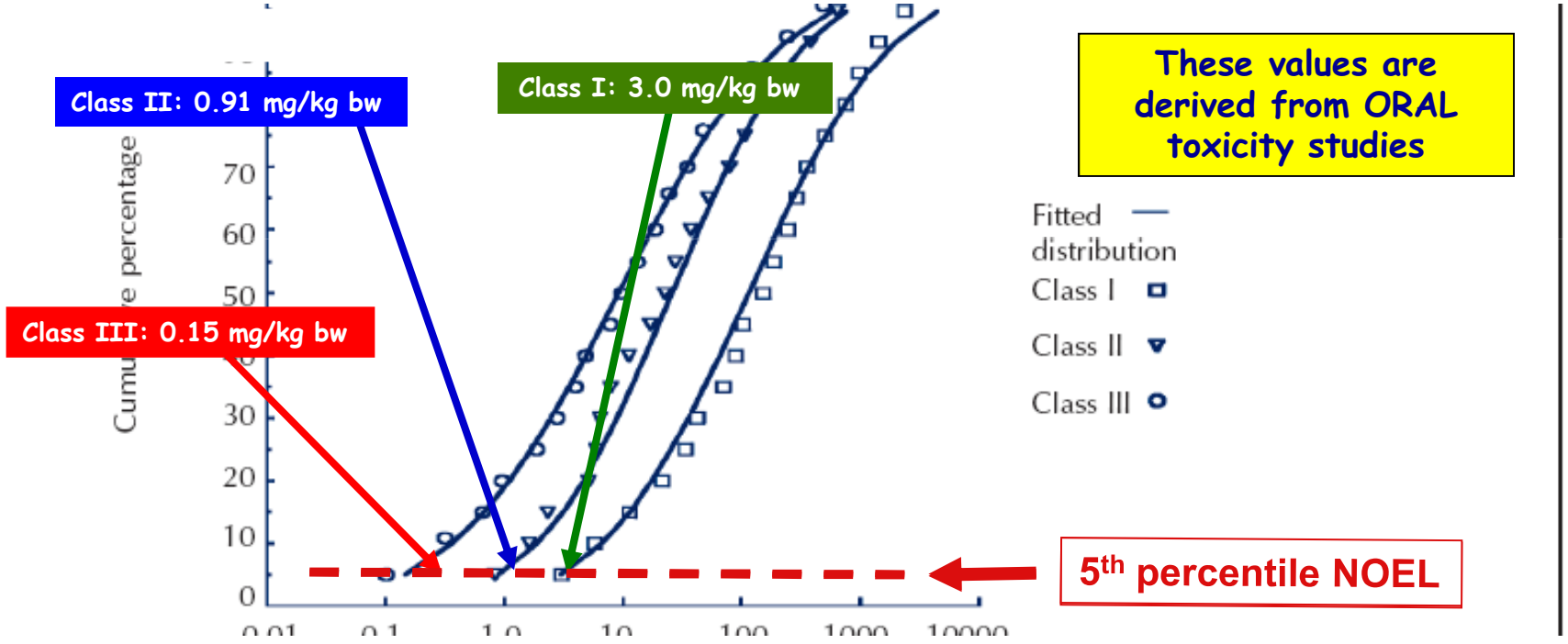
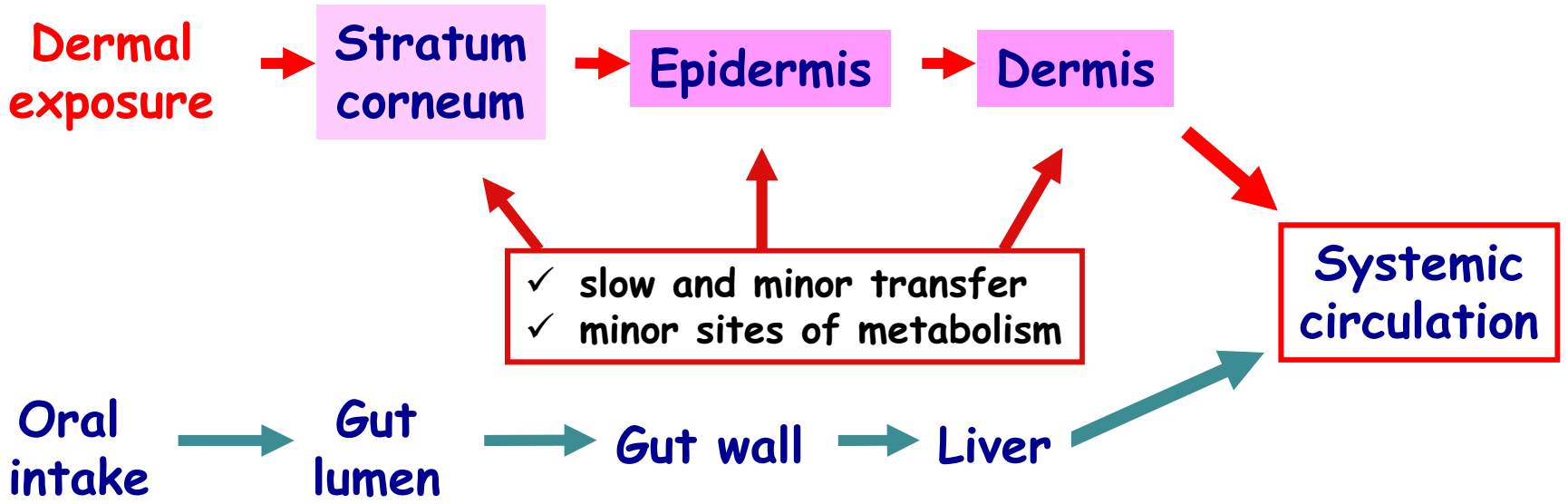
Kroes et al. FCT 2007

DOES THE ROUTE OF EXPOSURE ALTER THE POTENTIAL FOR METABOLIC DETOXICATION/BIOACTIVATION AND VALIDITY OF THE TTC/NOAELS?



COULD TOPICAL APPLICATION AFFECT THE ABSORBED FRACTION THAT IS CONVERTED TO INACTIVE OR TOXIC METABOLITES COMPARED TO ORAL ADMINISTRATION?



Slow intravenous infusion is closer to dermal exposure than oral administration!

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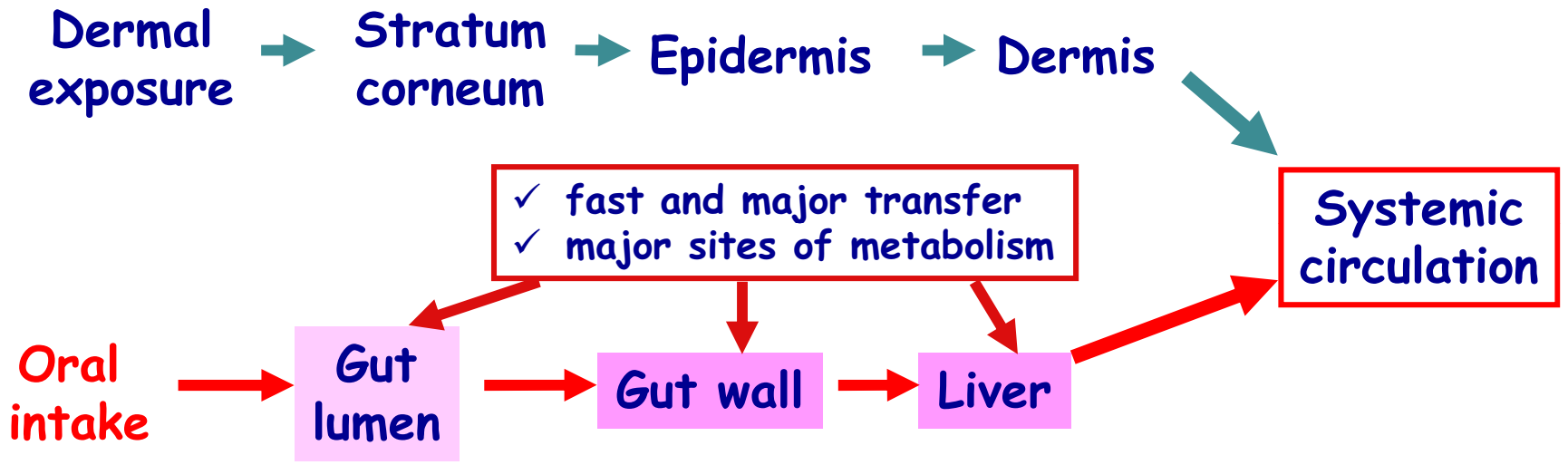

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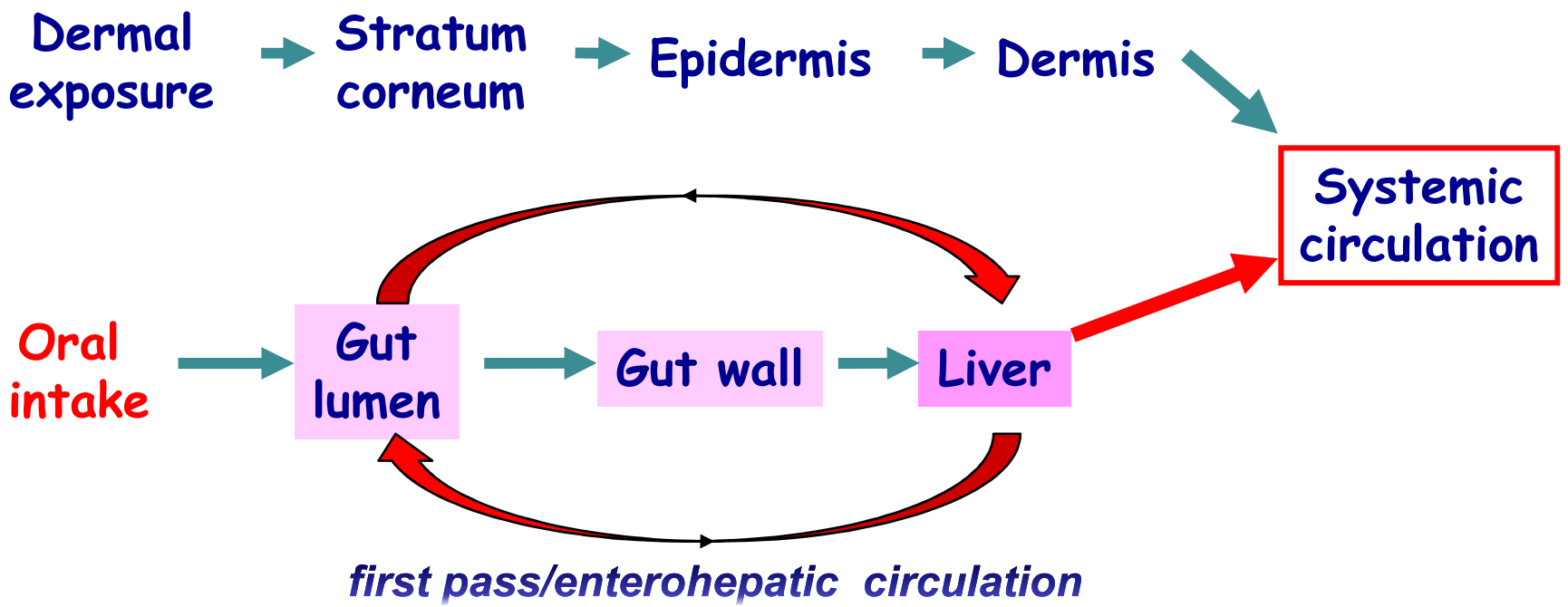

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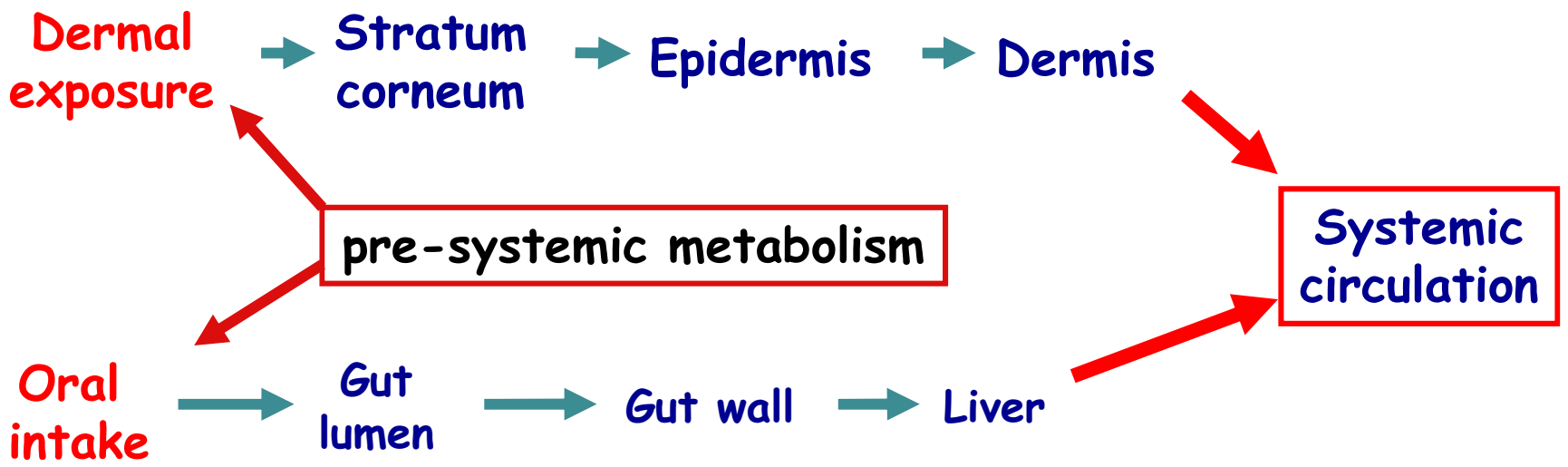

HUMAN DERMAL VS. ORAL EXPOSURE

Skin metabolic capacity less than in the liver and in the gutwall

Liver produces the same, and often additional metabolites than skin

In all known cases, oral administration produces higher plasma values and greater systemic exposure than dermal administration

Oral toxicity data may be used for risk assessment of dermal exposure (but not vice versa).

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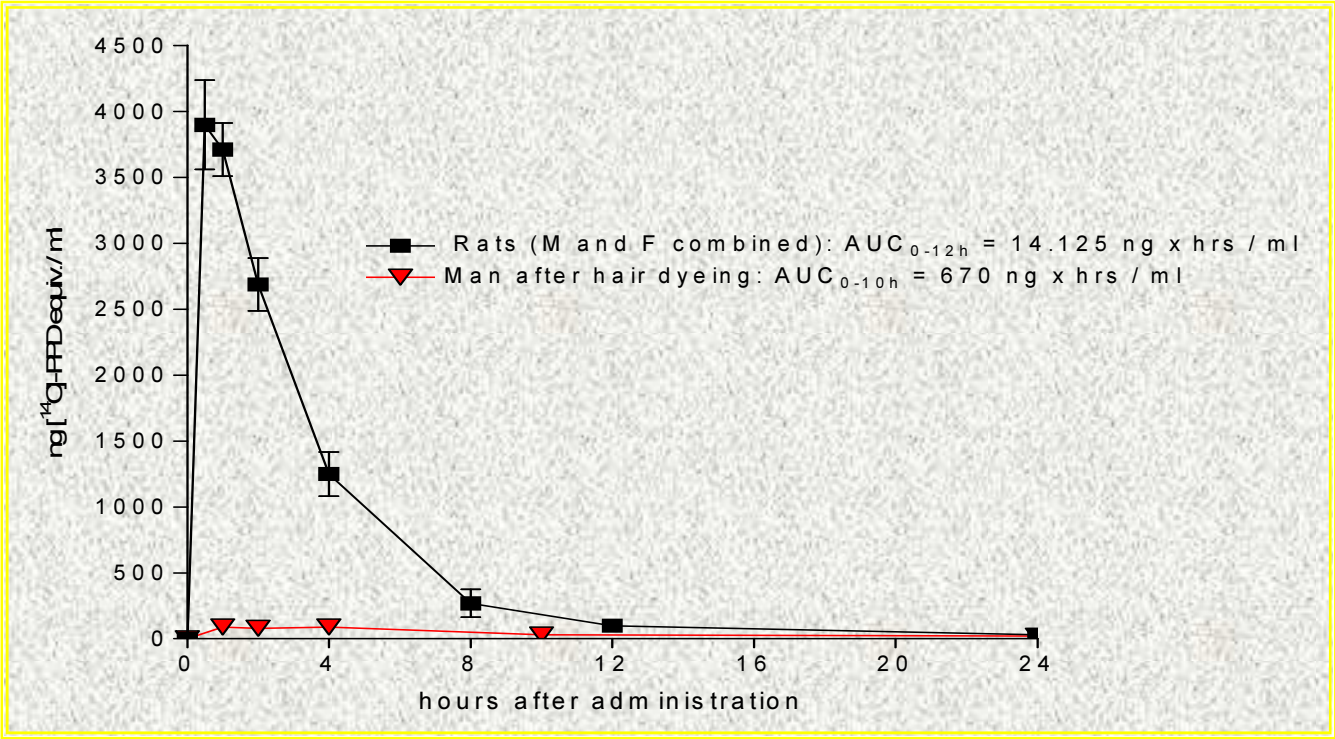
PATTERN OF SYSTEMIC (INTERNAL) EXPOSURE AFTER ORAL AND TOPICAL TREATMENT

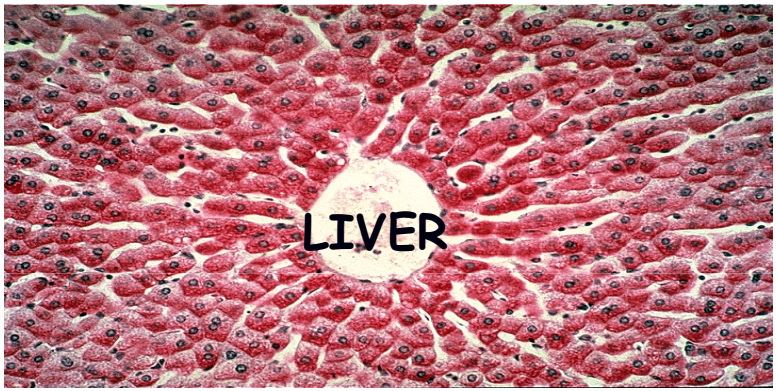


HOW CAN A TTC-APPROACH TAKE INTO ACCOUNT THE DERMAL ROUTE OF HUMAN EXPOSURE TO COSMETICS

Toxicity of topically applied substances is generally lower than that after oral administration, even when standardised to bioavailability.

- Due to different kinetics (lower Cmax / AUC values)
- Growing evidence for metabolism of certain cosmetic ingredients in the skin (aromatic amines in hair dyes)
- Although oral doses may be detoxified by first pass effects (liver), skin has a substantial metabolic capacity (esterases, N-acetyl transferases, CYPs)

PAP: METABOLISM IN HUMAN SKIN AND HEPATOCYTES SOME DIFFERENCES IN SKIN AND LIVER METABOLISM



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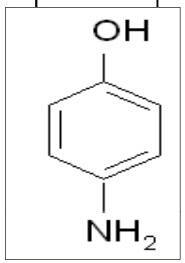
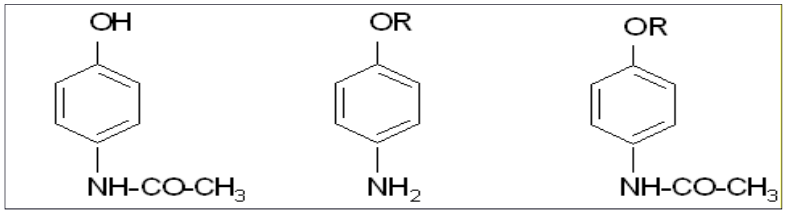
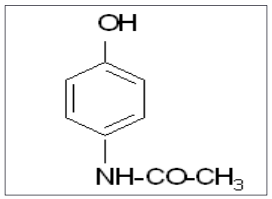


para-Aminophenol



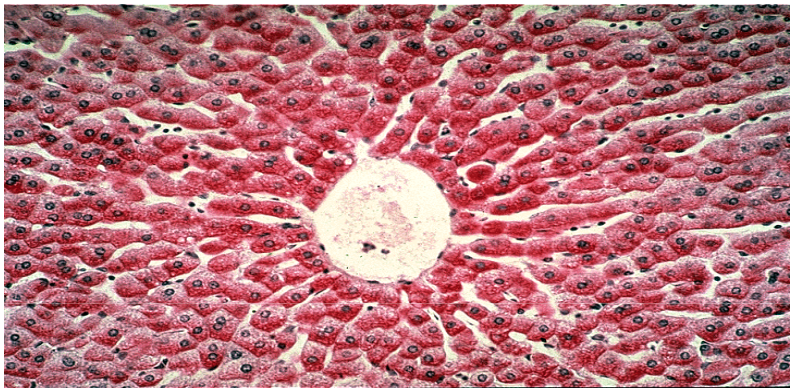
APAP *PAP-CONJ* *APAP-CONJ*



APAP only

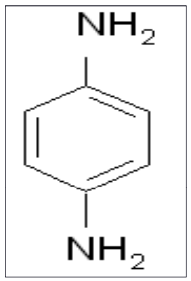
PPD: METABOLISM IN HUMAN SKIN AND HEPATOCYTES

SIMILAR METABOLISM, BUT SKIN AND LIVER HAVE DIFFERENT CAPACITY AND SPECIFICITY

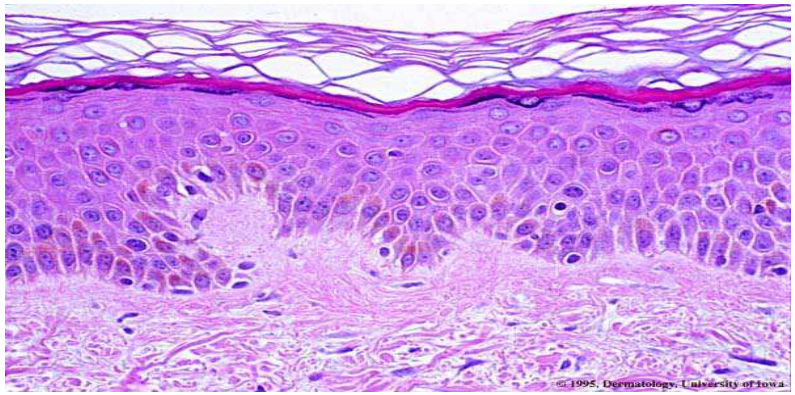


LIVER

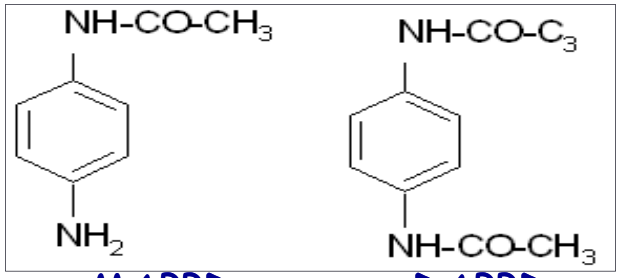
PPD



Para-Phenylenediamine



SKIN



MAPPD DAPPD

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Kroes et al. FCT 2007

PERCUTANEOUS PENETRATION

Percutaneous absorption depends on

- physical / chemical parameters of a substance, such MW and P_{ow} rate of diffusion, area and time
  - difference in the rates of absorption
- dermal/oral (presystemic metabolism)
  - different balance of parent compound and metabolites
  - difference in pathways of metabolism

Kroes et al. FCT 2007

THE MAXIMUM FLUX ACROSS THE SKIN

(Jmax in μg/cm²/hour)

Jmax can be related to the permeability coefficient Kp (cm/h) and the saturation solubility in the water

$$J_{max} = K_p * C^{sat}_{water}$$

Estimated experimentally

$$\log K_p = -2.7 + 0.71 * \log P - 0.0061 * MW$$

P = octanol-water partition coefficient of the chemical - MW = molecular weight

Kroes et al. FCT 2007

THE MAXIMUM POTENTIAL ABSORPTION - (Q_{abs} in μg)

$$Q_{abs} = J_{max} * A * T_{exp} * DS$$

J_{max} = the maximum flux across the skin for that chemical

A = the area of the skin in contact with the formulation (cm^2)

T_{exp} = the duration of the exposure (h)

$$DS = \frac{C_{vehicle}}{C^{sat}_{vehicle}}$$

DS = is the ratio of the actual concentration o the chemical in the vehicle to its saturation solubility in that vehicle and has a maximum value of 1 (for saturated solution).

Kroes et al. FCT 2007

CLASSIFICTION OF CHEMICALS IN TERMS OF THEIR POTENTIAL TO BE ABSORBED ACROSS THE SKIN

J_{MAX} - FLUX ($\mu g/cm^2/hour$)	MOLECULAR WEIGHT (Da)	log P_{OW}	% max. absorption
$J_{MAX} = 0$	>1000	any	Negligible
$J_{MAX} < 0.1$	>300	<-1 or >5	<10
$0.1 < J_{MAX} < 1.0$	~ 200 – 300	> 2.0 – 2.5	<10
$1.0 < J_{MAX} < 10.0$	~ 150 – 250	~ 1.0 – 2.0	<20
$10.0 < J_{MAX} < 100.0$	~ 60 – 200	~ 0.5 – 3.5	<40
$J_{MAX} > 100$	<150	-0.5 – 2.0	<80

Kroes et al. FCT 2007

PROPOSED DEFAULT ADJUSTMENT FACTORS FOR THE % DOSE ABSORBED OF COSMETIC INGREDIENT ACROSS THE SKIN

Jmax ($\mu g/cm^2/hr$)	Default % Dose Absorbed (24 hrs)
Non-reactive chemicals above 1000 Dalton	Negligible
Jmax < 0.1	10%
$0.1 < J_{MAX} < 1.0$	40%
Jmax > 10	80%

Kroes et al. FCT 2007

ASSUMPTIONS

- the compound is applied at its saturation concentration in the formulation (that the flux will be less than Jmax);
- no depletion of the chemical within the formulation occurs during the period of exposure (T_{exp}) (whereas in fact cosmetic ingredients are usually applied in concentration gradient (driving force) for transfer cross the skin);
- the formulation does not affect the characteristics of the skin barrier;
- by using the maximal flux over the entire exposure time, the lower flux during diffusional lag time is ignored.

CONCLUSIONS

- The TTC concept is not black magic box, but a validated scientific concept
- The Expert Group concluded that the TTC concept may be applied to the safety evaluation of cosmetic ingredients
- Use of the TTC would avoid unnecessary animal tests and aid priority setting of safety evaluations (evaluation of gram- instead of microgram-exposures)
- Recommendation of the expert group have been submitted to the Directorate-General for Health and Consumers (DG SANCO) and published in *Food Chemical Toxicology*

TTC ANALYSIS OF KNOWN CALENDULA (Dry Petal) CONSTITUENTS WITH KNOWN %							
	CAS number	(ToxTree)	Molecular Weight	Calculated Log KOW	Estimated Jmax	Default % Absorption	Systemic Exposure (ug/day)1
FLAVONOIDS <1.5%							
astragalin	480-10-4	3 (90 ug/day)	448,378	0.49 ± -1.11			
hyperoside	482-36-0	3 (90 ug/day)	464,377	0.30 ± -1.34			
isoquercitrin	21637-25-2	3 (90 ug/day)	464	-0,1	Jmax <0.1	10	<27
isorhamnetin	480-19-3	3 (90 ug/day)	316,264	2.39 ± 0.54	Jmax <0.1	10	<27
kaempferol	520-18-3	3 (90 ug/day)	286	1,96	0.1 <J max <10	40	<108*
neohesperidin (Closest Match to Neoliesperoside)	13241-33-3	3 (90 ug/day)	610,562	-0.05 ± 1.60	Jmax <0.1	10	<27
narcissin	604-80-8	3 (90 ug/day)	624,545	-0.45 ± 1.35	Jmax <0.1	10	<27
quercetin	117-39-5	3 (90 ug/day)	302,237	1,48	0.1 <Jmax <10	40	<108*
rutin	153-18-4	3 (90 ug/day)	610.518.	-2,02	Jmax <0.1	10	<27
syringenin (Closest Match to Syringentin)	118-34-3	3 (90 ug/day)	372,368	-0.45 ± 1.35	Jmax <0.1	10	<27
typhaneoside	104472-68-6	3 (90 ug/day)	770,686	7.57 ± 1.23	Jmax <0.1	10	<27
TANNINS 6 - 10%							
pyrogallol	87-66-1	1 (1800 ug/day)	126,11	0,97	Jmax >10	80	1440
catechol	120-80-9	1 (1800 ug/day)	110,111	0,88	Jmax >10	80	1440
FREE & ESTERIFIED TRITERPENIC ALCOHOLS <5%							
arnidiol	6750-30-7	1 (1800 ug/day)	442,723	7.57 ± 1.23	Jmax <0.1	10	<90
calenduladiol	10070-48-1	1 (1800 ug/day)	442,723	7.65 ± 1.17	Jmax <0.1	10	<90
erythrodiol	545-48-2	1 (1800 ug/day)	442,723	7.71 ± 0.76	Jmax <0.1	10	<90
faradiol	20554-95-4	1 (1800 ug/day)	442,723	7.53 ± 0.87	Jmax <0.1	10	<90
longispinogenin	465-94-1	3 (90 ug/day)	472,7488	6.91 ± 0.76	Jmax <0.1	10	<90
lupeol	545-47-1	1 (1800 ug/day)	426,724	9,23	Jmax <0.1	10	<90
maniladiol	595-17-5	1 (1800 ug/day)	442,723	7.55 ± 0.62	Jmax <0.1	10	<90
pseudotaraxasterol or psi-Taroxosterol	464-98-2	1 (1800 ug/day)	426,724	8.91 ± 1.31	Jmax <0.1	10	<90
taraxasterol	1059-14-9	1 (1800 ug/day)	426,724	8.69 ± 1.46	Jmax <0.1	10	<90
ursodiol	128-13-2	3 (90 ug/day)	392,576	3,00	?		
alpha-amyrin	638-95-9	1 (1800 ug/day)	426,724	9,16	Jmax <0.1	10	<90
TRITERPENIC GLYCOSIDES 2 - 10%							
calenduloside B (8CI)	34381-98-1	3 (90 ug/day)	943,126	2.49 ± 2.46			
1- Based upon full body application of 18 g of formulas/day, 0.1% concentration of dry petal, and UNITIS concentration of the chemical in the extract.							

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MAXIMUM ALLOWABLE % IN A NEW FORMULATION

PRODUCT TYPE	ESTIMATED DAILY AMOUNT APPLIED (G) SCCS/150/12	RETENTION FACTOR SCCS/150 /12	ABSORBTION RATE (%) Kroes, et al - maximal skin absorption = 80%	CALCULATED DAILY EXPOSURE (G/DAY)	MAXIMUM ALLOWABLE % IN FORMULA TO OBTAIN EXPOSURE OF:		
					180 µgG/DAY	540 µgG/DAY	1800 µgG/DAY
SKIN CARE							
BODY LOTION	7,82	1	80	6,26	0,003	0,009	0,03
FACE CREAM	1,54	1	80	1,23	0,015	0,045	0,15
HAND CREAM	2,16	1	80	1,73	0,01	0,03	0,1
HAIR CARE							
SHAMPOO	10,46	0,01	80	0,084	0,21	0,66	2,1
RINCE -OFF CONDITIONER	3,92	0,01	80	0,03	0,57	1,72	5,7
STYLING	4	0,1	80	0,32	0,056	0,17	0,56
MAKE-UP							
LIQUID FOUNDATION	0,51	1	80	0,41	0,04	0,12	0,4
EYE SHADOW	0,02	1	80	0,016	1,23	3,83	12,3
MASCARA	0,025	1	80	0,02	0,9	2,7	9
EYE LINER	0,005	1	80	0,004	4,5	13,5	45
LIPSTICK	0,057	1	100	0,057	0,32	0,95	3,2
DEODORANT							
NON-SPRAY	1,5	1	80	1,2	0,015	0,045	0,15
ORAL HYGIENE							
TOOTHPASTE	2,75	0,05	100		0,13	0,39	1,3
MOUTHWASH	21,62	0,1	100	2,162	0,008	0,025	0,08
SUNSCREEN							
FACE & BODY	18	1	0,8	14,4	0,00125	0,00375	0.0125

JUNIPER BERRY OIL
(JUNIPERUS COMMUNIS FRUIT OIL)

Assuming application of 18 g product/day,

an oil concentration of 0.2%

maximum absorption rate of 80%

the following can be eliminated from further analysis:

a - if class I and concentration is <6.25%

b - if class II and concentration is <1.875%

c - if class III and concentration is <0.625%

Molecule Name	CAS Number	Molecular Weight (g/mol)	% Range	Toxicity Class (ToxTree)
alpha-Pinene	80-56-8	136,236	20 - 80.4	I
alpha-Terpineol	98-55-5	154,251	0.1 - 6.0	III
beta-Caryophyllene	87-44-5	204,355	0.91 - 10.32	I
beta-Pinene	127-91-3	136,236	0.8 - 5.60 a	I
Borneol	507-70-0	154,251	<0.1-8	I
Bornyl acetate	76-49-3	196,288	0.2 - 3.21 a	I
Camphene	79-92-5	136,236	0.19 - 0.89 a	I
Carvacrol	499-75-2	150,220	0.25 - 0.45 a	I
Carvone	99-49-0	150,220	0.2 b	II
Caryophyllene oxide	1139-30-6	220,354	0 - 1.6 a	I
dl-Citronellol	106-22-9	156,267	0 - 1.3 a	I
Germacrene D	37839-63-7	204,355	6.50 - 14.31	I
Limonene	138-86-3	136,236	1.06 - 10.6	I
Linalool	78-70-6	154,251	0.1 - 1.3	III
Myrcene	123-35-3	136,236	0.68-46.3	I
Nerol	106-25-2	154,251	0.18 - 2.21 a	I
Sabinene	3387-41-5	136,236	1.53 - 36.8	I
Terpinolene	586-62-9	136,236	0.4-4 a	I

JUNIPER BERRY OIL
(JUNIPERUS COMMUNIS FRUIT OIL)

Physiochemical Properties of Juniper Oil (Juniperus communis L.) and Systemic Exposure

Congeneric Group	Molecule Name	CAS Number	Molecular Weight (g/mol)	log K_{ow}	Estimated % Penetration	Max % Conc. in oil	Tox Class (ToxTree /JEFCA)	Maximum Systemic Exposure µg/day 0.2% (18 g/day)	NOEL	MOS
Aliphatic & Alicyclic Hydrocarbons	alpha-Pinene	80-56-8	136,236	4,83	80,00	80,40	I	23155 a	300,00	777,00
	beta-Caryophyllene	87-44-5	204,355	6,30	40,00	10,32	I	1486		
	d-Limonene	5989-27-5	136,236	4,57	80,00	10,60	I	3053 a		
	Germacrene D	37839-63-7	204,355	6,99	40,00	14,31	I	2061 a		
	Myrcene	123-35-3	136,236	4,17	80,00	46,30	I	13334 a	250,00	1125,00
	Sabinene	3387-41-5	136,236	4,69	80,00	36,80	I	10598 a	300,00	1698,00
Monocyclic & Bicyclic Secondary Alcohols, Ketones & Related Esters	Borneol	507-70-0	154,251	2,69	80,00	8,00	I	2304 a		
Tetrahydrofuran and furanone derivatives	Linalool	78-70-6	154,251	2,97	80,00	0.1-1.3	III	374 a		
Aliphatic Branched-Chain Saturated & Unsaturated Alcohols, Aldehydes & Related Esters	alpha-Terpineol	98-55-5	154,251	2,98	80,00	6,00	III	1728 a		

a- Value exceeds TTC maximum systemic exposure level

TTC APPLICATIONS

- **Migrant** substances from packaging materials (USFDA-TOR- 1993)
- **Flavourings** substances in food (WHO-JECFA 1993,1995,1999….)
- Endorsed for the risk assessment of chemicals (WHO-IPCS 1998)
- Non relevant **plant protection product metabolites** in ground water (EC-2002)
- **Genotoxic impurities** in pharmaceutical preparations (EMA 2003,2004)
- **Flavourings** substances in food (EFSA 2004)
- **Genotoxic constituents** in herbal preparations (EMA 2006)
- Suggested for **REACH** (Registr, Evaluat, Authoriz and restrict of Chemical substances) (ECHA 2008)

- Suggested for application to **aquatic environmental** exposure (2005)
- Suggested for application to the **cosmetic ingredients** and their impurities (2007)
- Suggested for **prenatal developmental** toxicity (2010)
- **SUGGESTED FOR MIXTURE OF SUBSTANCES POTENTIALLY DETECTABLE IN SURFACE WATER (2011)**
- Suggested for risk prioritization of **trace chemicals in food**. *(2011)*

EXAMPLE CASE-STUDY A:
TIER 0 – SUBSTANCES POTENTIALLY DETECTABLE IN SURFACE WATER

- **10 compounds** potentially detectable in surface water, assuming that no toxicological information, other than structure, is available, were classified into Cramer Classes

- TTC values for each substance assigned
  - Cramer Class I (1800 µg/day = 0.0300 mg/kg b.w. day)
  - Cramer Class II (540 µg/day = 0.0091 mg/kg b.w. day)
  - Cramer Class III (90 µg/day = 0.0015 mg/kg b.w.day)

- **Exposure** (mg/kg b.w. day) = Surface water concentration (mg/L) x 0.42 L day/18 Kg (children)
  (Drinking water assumption made for children to be conservative)

- **Hazard Quotient (HQ)** for each substance = Exposure/TTC value

EXAMPLE CASE-STUDY A: TIER 0 – SUBSTANCES POTENTIALLY DETECTABLE IN SURFACE WATER

COMPOUND	EXPOSURE (mg/kg-bw/day)	TTC VALUE (mg/day)	TTC VALUE (mg/kg-bw/day)	HAZARD QUOZIENT (HQ) BASED ON TTC
A	1.94E-06	0.546	0.0091	2.1E-04
B	1.77E-06	0.090	0.0015	1.2E-03
C	8.87E-05	0.546	0.0091	9.7E-03
D	3.97E-05	1.800	0.0300	1.3E-03
E	3.03E-06	0.090	0.0015	2.0E-03
F	4.20E-06	0.090	0.0015	2.8E-03
G	7.93E-04	0.546	0.0091	8.7E-02
H	6.53E-06	1.800	0.0300	2.2E-04
I	1.42E-04	0.090	0.0015	9.5E-02
J	2.57E-05	1.800	0.0300	8.6E-04
HAZARD INDEX				0.2

The calculated **Hazard Index of 0.2 is less than 1.0**, and therefore the results of this Tier 0 assessment would suggest that advancement to higher assessment tiers is not necessary in this case.

MARGIN OF SAFETY
AND
SYSTEMIC EXPOSURE DOSAGE

MARGIN OF SAFETY (MoS)

$$MoS = \frac{NO(A)EL}{SED}$$

The MoS value is used to extrapolate from a group of test animals to an average human being, and subsequently from average humans to sensitive subpopulations.

The **WHO proposes a minimum value of 100**, and it is generally accepted that the **MoS should at least be 100 to conclude that a substance is safe for use**.

DERMAL ABSORPTION REPORTED AS A PERCENTAGE OF THE AMOUNT OF SUBSTANCE APPLIED

$$SED = A\ (mg/kg\ bw/day) \times C\ (\%)/100 \times DAp\ (\%)/100$$

SED (mg/kg bw/day) = Systemic Exposure Dosage

A* (mg/kg bw/day) = Estimated daily exposure to a cosmetic product per kg body weight, based upon the amount applied and the frequency of application: see the calculated relative daily exposure levels for different cosmetic product types.

C (%) = the Concentration of the substance under study in the finished cosmetic product on the application site

DAp (%) = Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real- life conditions

*data given

CALCOLO DELLA (SED) DERIVANTE DALL'ESPOSIZIONE ALLA M-CLOROANILINA NEL PRODOTTI UTILIZZATI PER PRATICHE DI TATUAGGIO E TRUCCO PERMANENTE

Quantità massima di prodotto applicato	=	1mL/1g
Percentuale media di m-cloroanilina in trucco p.	=	0,00072 %
Dose di m-cloroanilina	=	0,072 mg
Assorbimento cutaneo (caso peggiore 100%)	=	100 %
m-cloroanilina assorbita	=	0,072 mg
Peso corporeo medio individuo adulto	=	60 kg

SED = $(1*10^3$ mg/anno * 0,00072/100 * 100/100) / 60kg = 0,00012 mg/kg p.c.

CALCOLO DEL MoS DERIVANTE DALL'ESPOSIZIONE ALLA M-CLOROANILINA NEL PRODOTTI UTILIZZATI PER PRATICHE DI TATUAGGIO E TRUCCO PERMANENTE

$$MoS = \frac{5 \text{ mg/kg b.w.}}{0{,}00012 \text{ mg/kg b.w.}} = 41.166$$

DERMAL ABSORPTION OF TEST SUBSTANCE REPORT IN $\mu g/cm_2$

$$\mathbf{SED} = \mathbf{Da_a}\ (\mu g/cm_2) \times 10^{-3}\ mg/\mu g \times \mathbf{SSA}\ (cm^2) \times \mathbf{F}\ (day^{-1})/\mathbf{60\ kg}$$

SED (mg/kg bw/day) = Systemic Exposure Dosage

Da_a ($\mu g/cm_2$) = Dermal Absorption reported as amount/cm^2, resulting from an assay under in-use mimicking conditions

SSA* (cm^2) = *Skin Surface Area* expected to be treated with the finished cosmetic product

F* (day^{-1}) = *Frequency of application* of the finished product ($F \geq 1$)

60 kg = default human body weight

* data given

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

PRODOTTO COSMETICO FORMULATO CON IL 100% DEL SOLO COLORANTE CONTENENTE IL MASSIMO LIVELLO CONSENTITO DI CIASCUN METALLO PESANTE CONTEMPLATO DALLA LEGGE.

Metallo	Quantità massima teorica di metallo accettabile nei prodotti cosmetici (ppm)
Antimonio	100
Arsenico	5
Cadmio	5
Cobalto	70
Cromo III	100[(1)]
Cromo VI	25
Mercurio	1
Nichel	200
Piombo	20

[(1)] Quantità di Cromo(III) potenzialmente comprensivo dell'impurezze di Cromo(VI) che può raggiungere un valore massimo di 25 ppm. Il dato è valido per i prodotti cosmetici che non contengono coloranti a base di cromo.

Dati forniti da UNIPRO

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 1: Calcolo del MoS per l'**Antimonio**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento orale del metallo[4] (A)	SED (mg/kg p.c./giorno)	NOAEL (mg/kg p.c./giorno)	MoS[5] (NOAEL/SED)
fondotinta	0,51	1/giorno	0,51	100	0,01	5	0,0000425	0,6	14118
ombretto	0,01	2/giorno	0,02	100	0,01	5	0,0000017	0,6	360000
mascara	0,0125	2/giorno	0,25	100	0,01	5	0,0000021	0,6	288000
matita	0,0025	2/giorno	0,005	100	0,01	5	0,0000004	0,6	1440000
rossetto	0,0285	2/giorno	0,057	100	0,01	5	0,0000048	0,6	126316
polveri per il viso	0,25	2/giorno	0,5	100	0,01	5	0,0000417	0,6	14400

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

ARSENICO

$BMDL_{10}$: 0,0003 mg/kg p.c./giorno

L'EFSA Contaminant Panel ha modellato i dati dose-risposta sulla base di studi epidemiologici chiave, selezionando un intervallo di valori relativi al limite inferiore dell'intervallo di confidenza 95% di una risposta di riferimento di extra rischio dell'1% ($BMDL_{10}$). Per tumori al polmone, alla pelle e alla vescica e per le lesioni cutanee sono stati identificati valori di $BMDL_{10}$ compresi tra 0,3 e 8 µg/kg di peso corporeo al giorno (The EFSA Journal, 2009). E' stato quindi utilizzata la $BMDL_{10}$ più restrittiva di 0,3 ug/kg di peso corporeo al giorno relativo al parametro più sensibile i tumori polmonari riscontrati nella popolazione.

ASSORBIMENTO CUTANEO: 2%

Il dato di assorbimento utilizzato risulta da un arrotondamento per eccesso di un valore di assorbimento cutaneo del 1,9% ottenuto da uno studio *in vitro* su campioni di pelle umana (Wester et al., 1993). Nello stesso studio i valori di assorbimento cutaneo di arsenico applicato sulla pelle di scimmie Rhesus risultavano essere 6,4 e 2% rispettivamente per dosi diluite e concentrate.

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 2: Calcolo del MoS per l'**Arsenico**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento cutaneo del metallo (A)	SED (mg/kg p.c./giorno)	$BMDL_{10}$[5] (mg/kg p.c./giorno)	MoS[5] ($BMDL_{10}$/SED)
fondotinta	0,51	1/giorno	0,51	5	0,0005	2	0,000000850	0,0003	353
ombretto	0,01	2/giorno	0,02	5	0,0005	2	0,000000033	0,0003	9000
mascara	0,0125	2/giorno	0,25	5	0,0005	2	0,000000042	0,0003	7200
Matita	0,0025	2/giorno	0,005	5	0,0005	2	0,000000008	0,0003	36000
rossetto	0,0285	2/giorno	0,057	5	0,0005	2	0,000000095	0,0003	3158
polveri per il viso	0,25	2/giorno	0,5	5	0,0005	2	0,000000833	0,0003	360

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

CADMIO

BMDL$_5$: 0,0014 mg/kg p.c./giorno
L'EFSA Contaminant Panel ha calcolato il valore di BMDL$_5$ che produce un cambiamento specifico dei livelli urinari di B2M (beta-2-microglobulina) pari a 4 µg di cadmio/g creatinina nelle urine. Per rimanere al di sotto di 4 µg cadmio/g creatinina nelle urine, è stato calcolato che l'assunzione media giornaliera di cadmio nella dieta non dovrebbe superare 1,44 µg/kg di peso corporeo (The EFSA Journal, 2011).

ASSORBIMENTO CUTANEO: 0,8%
L'assorbimento cutaneo considerato è molto basso tra 0,3-0,8% (ATSDR, 1999).

Tabella 3: Calcolo del MoS per il **Cadmio**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento cutaneo del metallo (A)	SED (mg/kg p.c./giorno)	$BMDL_5$[6] (mg/kg p.c./giorno)	MoS[5] ($BMDL_5$/SED)
fondotinta	0,51	1/giorno	0,51	5	0,0005	0,8	0,000000340	0,0014	4118
ombretto	0,01	2/giorno	0,02	5	0,0005	0,8	0,000000013	0,0014	105000
mascara	0,0125	2/giorno	0,25	5	0,0005	0,8	0,000000017	0,0014	84000
Matita	0,0025	2/giorno	0,005	5	0,0005	0,8	0,000000003	0,0014	420000
rossetto	0,0285	2/giorno	0,057	5	0,0005	0,8	0,000000038	0,0014	36842
polveri per il viso	0,25	2/giorno	0,5	5	0,0005	0,8	0,000000333	0,0014	4200

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 4: Calcolo del MoS per il **Cobalto**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento orale del metallo[4] (A)	SED (mg/kg p.c./giorno)	NOAEL (mg/kg p.c./giorno)	MoS[5] (NOAEL/SED)
fondotinta	0,51	1/giorno	0,51	70	0,007	25	0,0001488	0,6	4034
ombretto	0,01	2/giorno	0,02	70	0,007	25	0,0000058	0,6	102857
mascara	0,0125	2/giorno	0,25	70	0,007	25	0,0000073	0,6	82286
matita	0,0025	2/giorno	0,005	70	0,007	25	0,0000015	0,6	411429
rossetto	0,0285	2/giorno	0,057	70	0,007	25	0,0000166	0,6	36090
polveri per il viso	0,25	2/giorno	0,5	70	0,007	25	0,0001458	0,6	4114

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

CROMO(III)

NOAEL: 1800 mg/kg p.c./giorno

Una RfD cronica orale di 1,5 mg di cromo(III)/kg p.c. al giorno è stata calcolata dall'Environmental Protection Agency americana EPA-USA per i sali insolubili di cromo(III). La RfD è basata su un NOAEL per effetti sistemici nel ratto alimentato con una dieta contenente 1800 mg di Cr_2O_3/kg peso corporeo per 840 giorni (Ivankovich e Preussmann 1975; IRIS 2008). La Reference Dose (RfD) è una dose di riferimento operativa derivata dal NOAEL mediante l'applicazione di Fattori di Sicurezza, ed è la dose a cui un uomo può essere esposto giornalmente senza che intervengano effetti dannosi per la salute.

ASSORBIMENTO ORALE: 2%

L'assorbimento intestinale di cromo(III) è stato valutato in un intervallo tra 0,5% e 2% (Davis et al., 2002; Anderson et al., 1985; Offenbacher et al., 1986).

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 5: Calcolo del MoS per il **Cromo(III)**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento orale del metallo[4] (A)	SED (mg/kg p.c./giorno)	NOAEL (mg/kg p.c./giorno)	MoS[5] (NOAEL/SED)
fondotinta	0,51	1/giorno	0,51	100	0,01	2	0,0000170	1800	105882353
ombretto	0,01	2/giorno	0,02	100	0,01	2	0,0000007	1800	2700000000
mascara	0,0125	2/giorno	0,25	100	0,01	2	0,0000008	1800	2160000000
matita	0,0025	2/giorno	0,005	100	0,01	2	0,0000002	1800	10800000000
rossetto	0,0285	2/giorno	0,057	100	0,01	2	0,0000019	1800	947368421
polveri per il viso**	0,25	2/giorno	0,5	100	0,01	2	0,0000167	1800	108000000

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

CROMO(VI)

NOAEL: 2,5 mg/kg p.c./giorno
Una RfD cronica orale di 0,003 mg di cromo(VI)/kg p.c. al giorno è stata calcolata e verificata dall'Environmental Protection Agency americana EPA-USA per i sali solubili di cromo(VI). La RfD è basata su un NOAEL per effetti sistemici nel ratto esposto a 2,5 mg di cromato di potassio in acqua da bere per 1 anno in uno studio condotto da MacKenzie et al. (1958).

ASSORBIMENTO ORALE: 3%
Nell'uomo solo una piccola frazione (0,5-3%) del cromo ingerito viene assorbito a livello gastrointestinale (Christensen, 1995; Paustenbach et al., 1996).

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 6: Calcolo del MoS per il **Cromo(VI)**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento orale del metallo[4] (A)	SED (mg/kg p.c./giorno)	NOAEL (mg/kg p.c./giorno)	MoS[5] (NOAEL/SED)
fondotinta	0,51	1/giorno	0,51	25	0,0025	3	0,0000064	2,5	392157
ombretto	0,01	2/giorno	0,02	25	0,0025	3	0,0000003	2,5	10000000
mascara	0,0125	2/giorno	0,25	25	0,0025	3	0,0000003	2,5	8000000
matita	0,0025	2/giorno	0,005	25	0,0025	3	0,0000001	2,5	40000000
rossetto	0,0285	2/giorno	0,057	25	0,0025	3	0,0000007	2,5	3508772
polveri per il viso	0,25	2/giorno	0,5	25	0,0025	3	0,0000063	2,5	400000

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 7: Calcolo del MoS per il **Mercurio**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento orale del metallo[4] (A)	SED (mg/kg p.c./giorno)	NOAEL (mg/kg p.c./giorno)	MoS[5] (NOAEL/SED)
fondotinta	0,51	1/giorno	0,51	1	0,0001	7	0,00000060	0,0015	2521
ombretto	0,01	2/giorno	0,02	1	0,0001	7	0,00000002	0,0015	64286
mascara	0,0125	2/giorno	0,25	1	0,0001	7	0,00000003	0,0015	51429
matita	0,0025	2/giorno	0,005	1	0,0001	7	0,00000001	0,0015	257143
rossetto	0,0285	2/giorno	0,057	1	0,0001	7	0,00000007	0,0015	22556
polveri per il viso	0,25	2/giorno	0,5	1	0,0001	7	0,00000058	0,0015	2571

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

NICHEL

NOAEL: 1,1 mg/kg p.c./giorno

In uno studio di due generazioni su ratti, è stato identificato un NOAEL di 1,1 mg di nichel per kg di peso corporeo al giorno per tutti gli end-point studiati, tra cui la letalità post-impianto/perinatale (SLI, 2000; UE, 2004).

ASSORBIMENTO CUTANEO: 2%

Studi *in vitro* su pelle umana hanno indicato un assorbimento cutaneo di nichel di meno del 2% che si riduce all'1% considerando la quantità di nichel fissata dalle cellule dello strato corneo della cute (HEALTH RISK ASSESSMENT GUIDANCE FOR METALS - HERAG 01, 2007; Tanojo et al., 2001).

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 8: Calcolo del MoS per il **Nichel**

make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento cutaneo del metallo (A)	SED (mg/kg p.c./giorno)	NOAEL (mg/kg p.c./giorno)	MoS[5] (NOAEL/SED)
fondotinta	0,51	1/giorno	0,51	200	0,02	2	0,0000340	1,1	32353
ombretto	0,01	2/giorno	0,02	200	0,02	2	0,0000013	1,1	825000
mascara	0,0125	2/giorno	0,25	200	0,02	2	0,0000017	1,1	660000
matita	0,0025	2/giorno	0,005	200	0,02	2	0,0000003	1,1	3300000
rossetto	0,0285	2/giorno	0,057	200	0,02	2	0,0000038	1,1	289473
polveri per il viso	0,25	2/giorno	0,5	200	0,02	2	0,0000333	1,1	33000

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

PIOMBO

$BMDL_{10}$: 0,00063 mg/kg p.c./giorno

La $BMDL_{10}$ per quanto riguarda gli effetti cardiovascolari pressori è 1,5 µg/kg p.c./giorno ed è stata stimata dall'esposizione al piombo tramite la dieta per consumatori adulti in Europa. La $BMDL_{10}$ per gli effetti renali è di 0,63 µg/kg p.c./giorno (The EFSA Journal, 2010).

ASSORBIMENTO CUTANEO: 0,3%

L'assorbimento percutaneo di piombo acetato da preparazioni coloranti dei capelli è risultato sostanzialmente zero con un range fra 0-0,3% della dose applicata sulla cute. Un moderato assorbimento era rilevabile in caso di epidermide danneggiata (Moore et al., 1980).

PRESENZA DI METALLI ALL'INTERNO DI PRODOTTI COSMETICI

Tabella 9: Calcolo del MoS per il **Piombo**

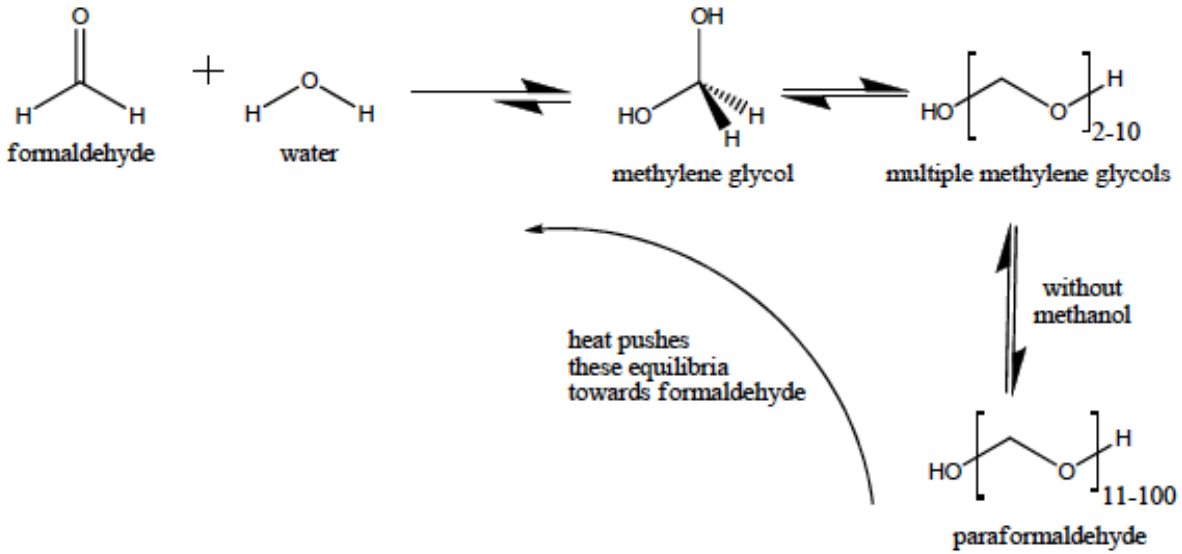
make-up	quantità per applicazione (g)[2]	frequenza di applicazione[2]	quantità applicata giornalmente (g/giorno)[2] (Q)	quantità massima di metallo presente nei prodotti cosmetici (ppm)[3]	% massima di metallo presente nei prodotti cosmetici (C)	% di assorbimento cutaneo del metallo (A)	SED (mg/kg p.c./giorno)	$BMDL_{10}$[6] (mg/kg p.c./giorno)	MoS[5] ($BMDL_{10}$/SED)
fondotinta	0,51	1/giorno	0,51	20	0,002	0,3	0,000000510	0,00063	12353
ombretto	0,01	2/giorno	0,02	20	0,002	0,3	0,000000020	0,00063	315000
mascara	0,0125	2/giorno	0,25	20	0,002	0,3	0,000000025	0,00063	252000
matita	0,0025	2/giorno	0,005	20	0,002	0,3	0,000000005	0,00063	1260000
rossetto	0,0285	2/giorno	0,057	20	0,002	0,3	0,000000057	0,00063	110526
polveri per il viso	0,25	2/giorno	0,5	20	0,002	0,3	0,000000500	0,00063	12600

USE OF FORMALDEHYDE/METHYLENE GLYCOL

IN HAIR SMOOTHING PRODUCTS

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

Scheme 1 – Equilibria in aqueous formaldehyde solutions such as formalin



USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

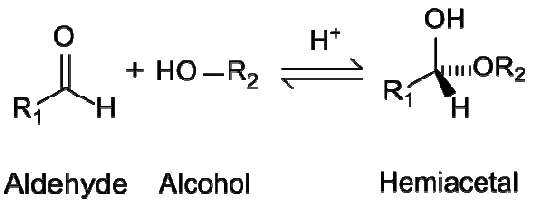
Formaldehyde (as part of a formalin solution) is known to induce a fixative action on keratin.

This is at least in accord with formaldehyde's function as a denaturant, in the classic sense of the term (ie, reacting with biological molecules, such as disrupting the tertiary structure of proteins).

Formaldehyde/methylene glycol hair straightening formulations, maintain straightened hair by altering protein structures via amino acid crosslinking reactions, which form crosslinks between hair keratins and with **added keratin from the formulation**.

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

- hemiacetal formation between a keratin hydroxyl group and formaldehyde,



Aldehyde Alcohol Hemiacetal

- reaction of two such hemiacetals, in a dehydration step, to form a methylene ether crosslink, and

- formaldehyde elimination to finalize the new methylene crosslink.

- Stoichiometricaly, this proposed scheme supports that some of the formaldehyde that initially reacts with keratin is eventually **released as formaldehyde during the hair straightening process**.

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

- Formalin, is an aqueous solution of formaldehyde, methylene glycol and polymethylene glycols, all in equilibria and often stabilized with methanol.

- "100% formalin" means an aqueous solution wherein formaldehyde has been added to water to the saturation point of these equilibria, which is typically 37% (by weight) formaldehyde equivalents in water.

- Formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde and 0.118% (w/w) calculated as methylene glycol.

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

- Formaldehyde does not penetrate beyond the superficial layer of the nasopharyngeal epithelium, and is unlikely to appear in the blood as an intact molecule, except possibly at concentrations high enough to overwhelm the metabolic capacity of the epithelium.

- There was no evidence that formaldehyde can induce neoplasia at concentration/time relationships that do not damage normal structure (cytotoxicity) and function of tissues, even under laboratory conditions: non-linear response.

- Endocrine disruptors, genotoxic, occupational exposure, limphoematopietic cancers ??

Formaldehyde can be a skin irritant and sensitizer, but at levels higher than the 0.2% free formaldehyde

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

endogenous formaldehyde in the blood

of rats, monkeys, and humans is about 0.1 mM

in exhaled breath formaldehyde is likely present normally

at concentrations of a few parts per billion (ppb)

in indoor air average of 0.016 to 0.032 ppm formaldehyde.

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

U.S. National Institute of Occupational Health NIOSH Recommended Exposure Limits

10-hour Recommended Exposure Limit (REL-TWA) 0.016 ppm

15-minute Recommended Short Term Exposure Limit (REL-STEL-TWA) 0.1 ppm

U.S. Occupational Safety & Health Administration Enforceable Standards

8-hour Threshold for Hazard Communication Requirements (Threshold-TWA) 0.1 ppm

8 hour Action Level (AL-TWA) 0.5 ppm

8-hour Permissible Exposure Limit (PEL-TWA) 0.75 ppm

15-minute Short Term Exposure Limit (STEL-TWA) 2 ppm

WHO

30-minute average indoor air guideline 0.08 ppm

USE OF FORMALDEHYDE/METHYLENE GLYCOL IN HAIR SMOOTHING PRODUCTS

- Concentrations in the 6 background samples ranged from 0.0068 to 0.032 ppm.
- Concentrations in the other 22 area samples ranged from <0.005 ppm for 45 minutes to 0.14 ppm for 73 minutes.
  - The 3 highest area concentrations (ranging from 0.084 ppm for 69 minutes to 0.14 ppm for 73 minutes) were collected during the treatments, and exceeded the WHO 30-minute guideline (0.08 ppm).
- Concentrations in 9 samples collected in **THE BREATHING ZONES** during the procedures **(INCLUDING APPLICATION OF THE PRODUCT, BLOW DRYING AND FLAT IRONING)** ranged from 0.11 ppm for 63 minutes to 0.33 ppm for 73 minutes.
  - The highest concentration (0.33 ppm) exceeded the ACGIH TLV® -C (0.3 ppm), and all of them exceeded the WHO 30-minute guideline (0.08 ppm) by up to 4 fold.
- Concentrations in the 26 samples collected in **THE BREATHING ZONES** during each of the separate steps the procedures ranged from 0.041 ppm for 43 minutes (**DURING FLAT IRONING**) to 0.76 ppm for 17 minutes (during blow drying).
  - The 4 highest concentrations (ranging from 0.66 for 20 minutes to 0.76 ppm for 17 minutes) were 73% to 84% of the U.S. NAC AEGL-1 (0.9 ppm).
  - Concentrations in 9 of the 26 samples (ranging from 0.31 ppm for 32 minutes to 0.76 for 17 minutes) exceeded the ACGIH TLV® -C (0.3 ppm) by up to 2.5 fold.
  - Concentrations in 6 of the 10 samples collected for 30 minutes or more during each step of the treatments (ranging from 0.084 ppm for 31 minutes to 0.31 ppm for 32 minutes) exceeded the WHO 30-minute guideline (0.08 ppm) by up to 4 times.

REFINING THE THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) FOR RISK PRIORITIZATION OF TRACE CHEMICALS IN FOOD

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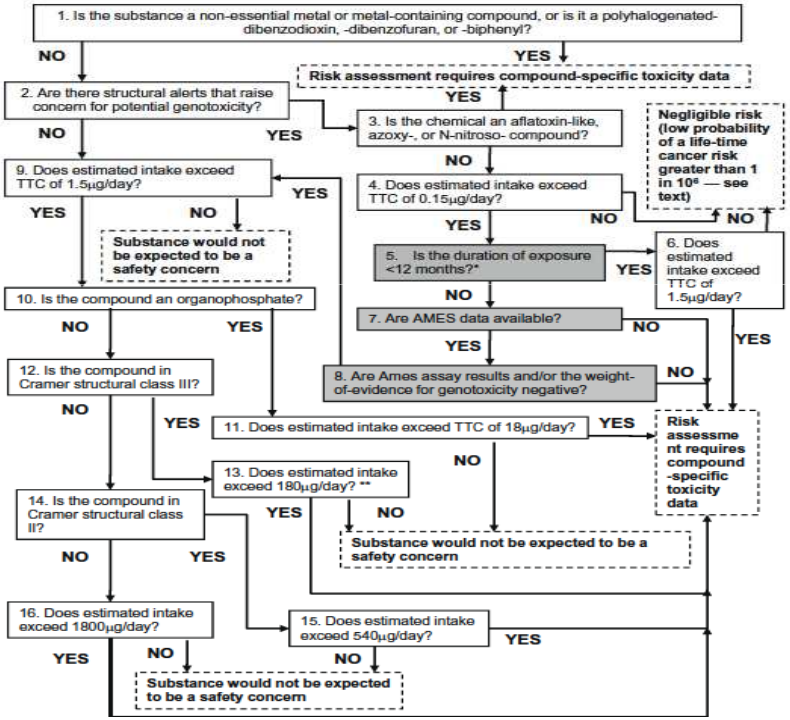

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