

Allergien gegen Haarfarben – Differenziert betrachtet aus der Sicht der klinischen Epidemiologie

Allergies to hair dyes –
a differentiated look from clinical epidemiology

Axel Schnuch
IVDK
Göttingen

BfR-Symposium Haarfarben 15. Oktober 2009

IVDK:

50 departments
of dermatology
in central Europe



EUROPEAN SURVEILLANCE SYSTEM ON CONTACT ALLERGIES (ESSCA)



32 departments
11 countries



Board of Directors

Uter/D, Stratham/UK, Schnuch /D

Number of departments  1-3

 4-6

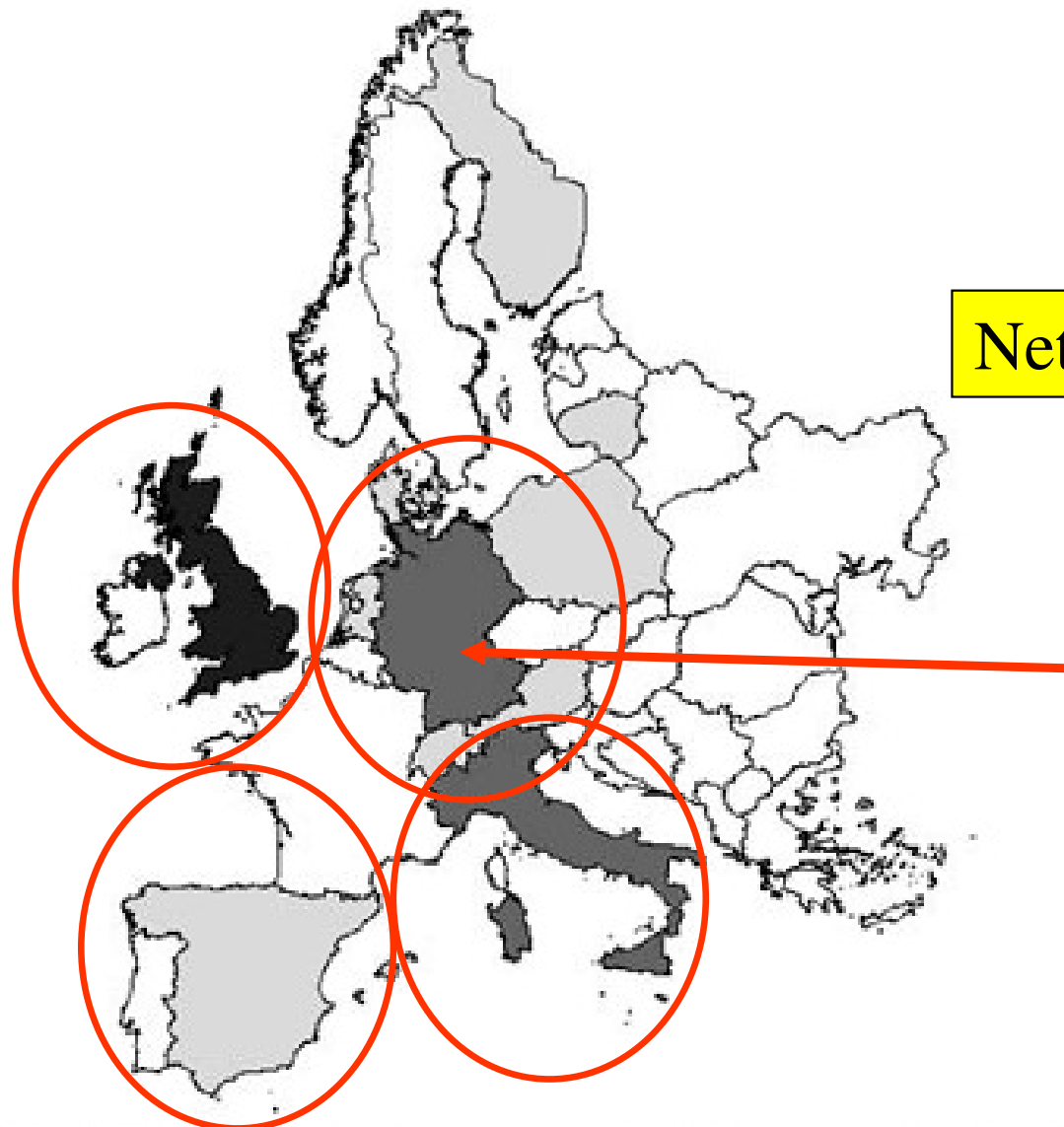
 7 or more

JEADV 22:174 (2008)

EUROPEAN SURVEILLANCE SYSTEM ON CONTACT ALLERGIES (ESSCA)



Network of (national) networks



Erlangen/D: Data centre

Number of departments  1-3

 4-6

 7 or more

EUROPEAN ENVIRONMENTAL
CONTACT DERMATITIS RESEARCH
(EECDRG)

and

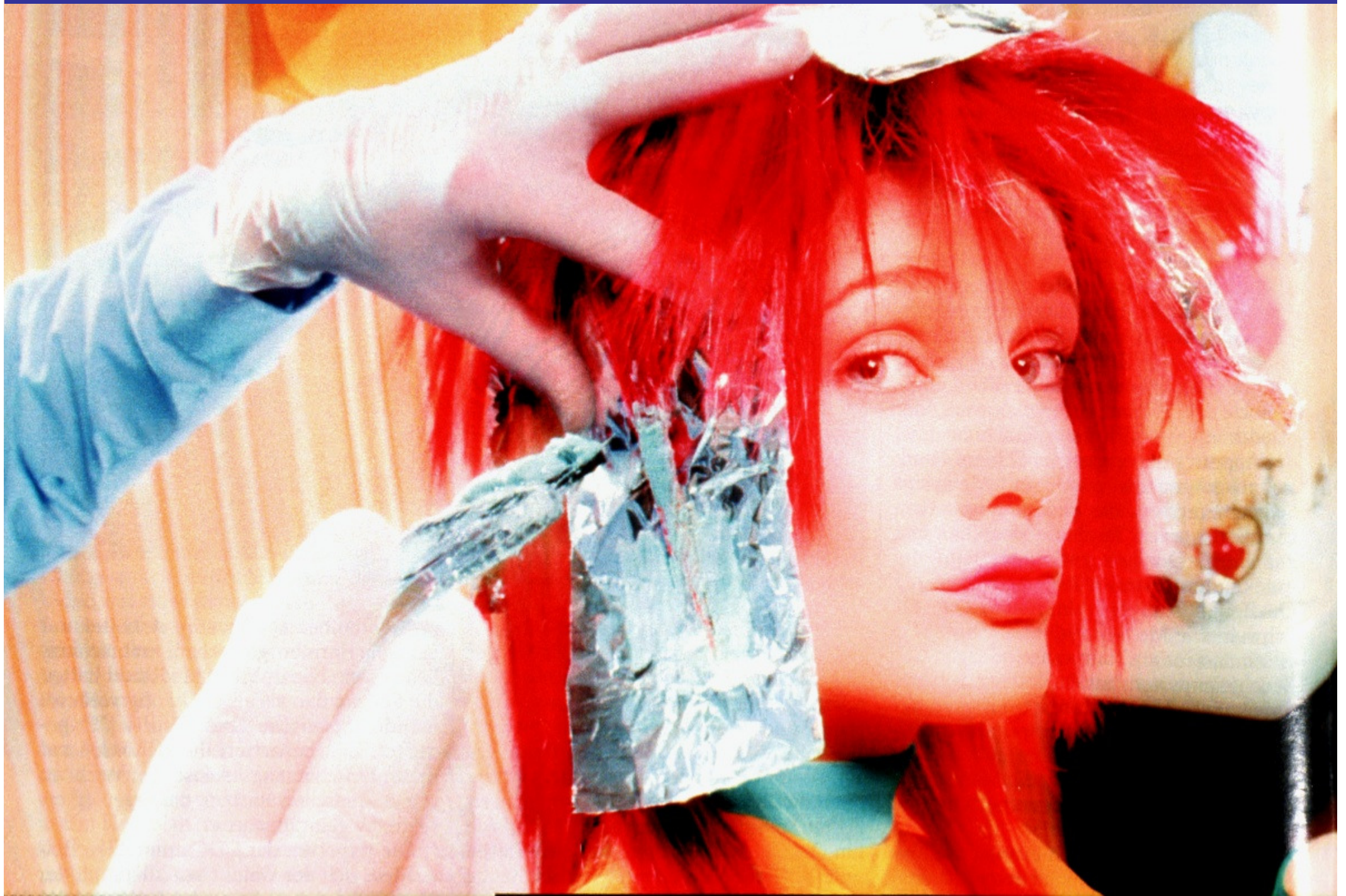
„Historical“ studies from various departments

Allergies to hair dyes –
a differentiated look from clinical epidemiology

OUTLINE:

1. Allergies to hair dyes
2. Allergies to para-phenylenediamine

The problem of HAIR DYEING



Hairdye components actually tested

DKG-hairdresser series

- Hydroquinone (1% petr)
- p-Toluylenediamine (1% petr)
- p-Aminophenol (1% petr)
- m-Aminophenol (1% petr)
- Resorcin (1% petr)
- Pyrogallol („historical“, 1% petr.)
- p-Phenylenediamine (1% petr.)*

*stand series

Contact allergy to ingredients of hair cosmetics in female hairdressers and clients – an 8-year analysis of IVDK* data

WOLFGANG UTER¹, HOLGER LESSMANN², JOHANNES GEIER² AND AXEL SCHNUCH²

Contact Dermatitis 49: 236 (2003)

Contact allergy to hairdressing allergens in female hairdressers and clients – current data from the IVDK, 2003–2006

Wolfgang Uter¹, Holger Lessmann², Johannes Geier², Axel Schnuch²

JDDG 5 : 993 (2007)

IVDK studies on female hairdressers and clients*

IVDK data 1995 – 2002
(n= 77,901)

IVDK data 2003 – 2006
(n= 37,929)

Study population

Hairdressers
+ occup. CD susp.

884

480

Never hairdressers;
hair cosmetics
suspected

1217

780

* home-users of hair cosmetics included

IVDK studies on female hairdressers and clients*

Results of study periods 1995 – 2002 and 2003 – 2006

	Clients	Hairdressers
Anatomical sites		
Head,face,neck	65.4%	3.5%
Hands	10.0%	89.3%

IVDK studies on female hairdressers and clients*

Results of study periods 1995 – 2002

Allergens*	Clients		Hairdressers
<i>p</i> -Toluylenediamine	13.9 %	↑	22.8 %
<i>p</i> -Aminophenol	7.2 %	↑	5.0 %
<i>m</i> -Aminophenol	4.6 %		3.0 %
GMTG	1.9 %		13.5 % ↓
<i>p</i> -Phenylenediamine	15.4 %	↑	18.7 %

*adjusted percentage

IVDK studies on female hairdressers and clients

Results of study periods 1995 – 2002 and 2003 – 2006

Allergens*	Clients	Hairdressers
<i>p</i> -Toluylenediamine	13.9 / 22.6 %	22.3 / 19.6 %
<i>p</i> -Aminophenol	7.2 / 11.9 %	5.0 / 5.7 %
<i>m</i> -Aminophenol	4.6 / 9.1 %	3.0 / 4.9 %
GMTG	1.9 / 1.6 %	13.5 / 9.8 %
<i>p</i> -Phenylenediamine	15.4 / 20.3** %	18.7 / 18.1 %

*adjusted percentage

IVDK studies on female hairdressers and clients

Results of study periods 1995 – 2002 and 2003 – 2006

Allergens*

p-Toluylenediamine

Clients

13.9 / **22.6** % ★

Hairdressers

22.3 / **19.6** %

p-Aminophenol

7.2 / **11.9** % ★

5.0 / 5.7 %

m-Aminophenol

4.6 / **9.1** % ★

3.0 / 4.9 %

GMTG

1.9 / 1.6 %

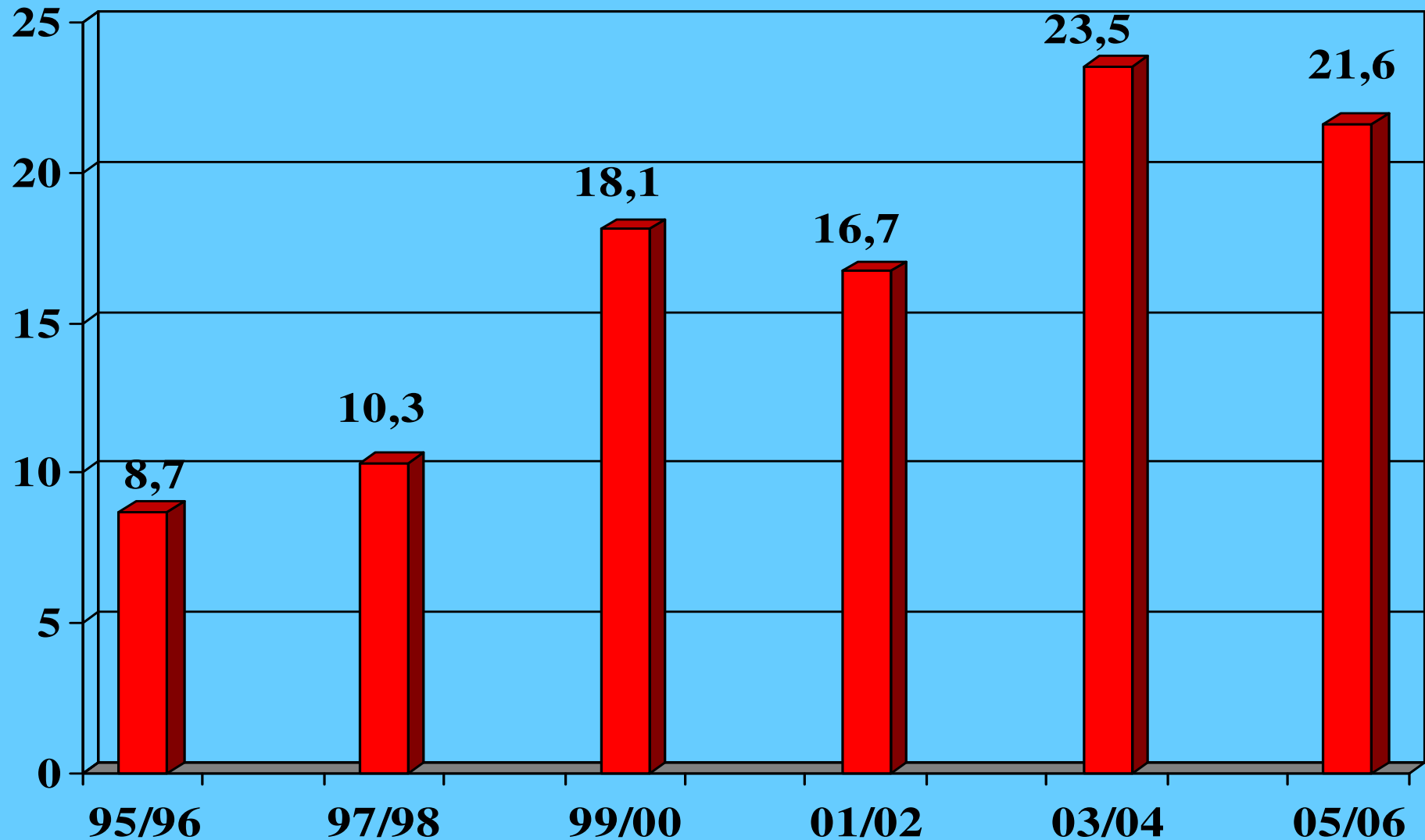
13.5 / 9.8 %

p-Phenylenediamine

15.4 / **20.3**** %

18.7 / 18.1 %

Sensitization to **p-Toluylenediamine** in clients (1995 – 2006)

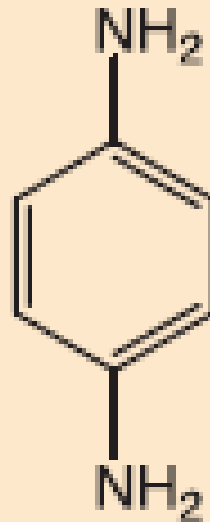


IVDK studies on female hairdressers and clients

Conclusion:

1. Sensitization to hair dye-related compounds increased significantly during the last decade in a selected group of patients
2. In this selected group sensitization to p-phenylenediamine is four times higher compared to an unselected patch test population

p-phenylenediamine



Scheme 6. *para*-Phenylenediamine

Most cases of contact allergy to PPD occur from contact with hair dyes, in either the consumer or the hairdresser [1]. In the United States, it is one of the

Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Contact Dermatitis, (Frosch PJ, Menne T, Lepoittevin J.-P., eds.) 4th edition. Berlin: Springer, 2006; 453-492.

p-Phenylenediamine (PPD)

1. Clinical epidemiology (international studies)
2. Clinical epidemiology (results from the IVDK)
3. Clinical epidemiology and population-based epidemiology:
the role of the CE-DUR model

Sensitization to paraphenylenediamine - international studies

Barcelona	1973 – 74	-	Romaguera / Grimalt 1980	6.1%
ICDRG	1967/68	-	Fregert et al 1980	4.9%
Zürich	1990-1994	↑	Bangha/Elsner 1996	4.3%
Nanjing	1988 – 1996	-	Liu 1997	8.0%
Hong Kong	1995 – 1999	-	Lam 2008	6.0%
NACDG	2001 – 2002	-	Pratt 2004	4.8%
NACDG	1970 – 2002	↓	Nguyen 2008	(8% → 4.8%)

Sensitization to paraphenylenediamine - international studies

Sweden	1992 – 2000	↑	Lindberg 2007 (m:1.3)	2.3%
Denmark	1985 – 2005	↑	Carlsen/Thyssen 2007/8	2.1%
Czech Republic	1997 – 2001	–	Machovcova 2005	2.0%
UK (7 centres)	2000	–	Britton 2003	3.0%
UK (St. John's)	1982 – 1998	–	Armstrong 1999	3.2%
UK (St. John's)	1999 – 2003	↑	Patel 2007	4.5%
UK (St. John's)	2004	↑	Patel 2007	7.1%

Leading anatomical sites:

Hands 35%

Face/Neck 27%

Leading occupations:

Hairdressers 19%

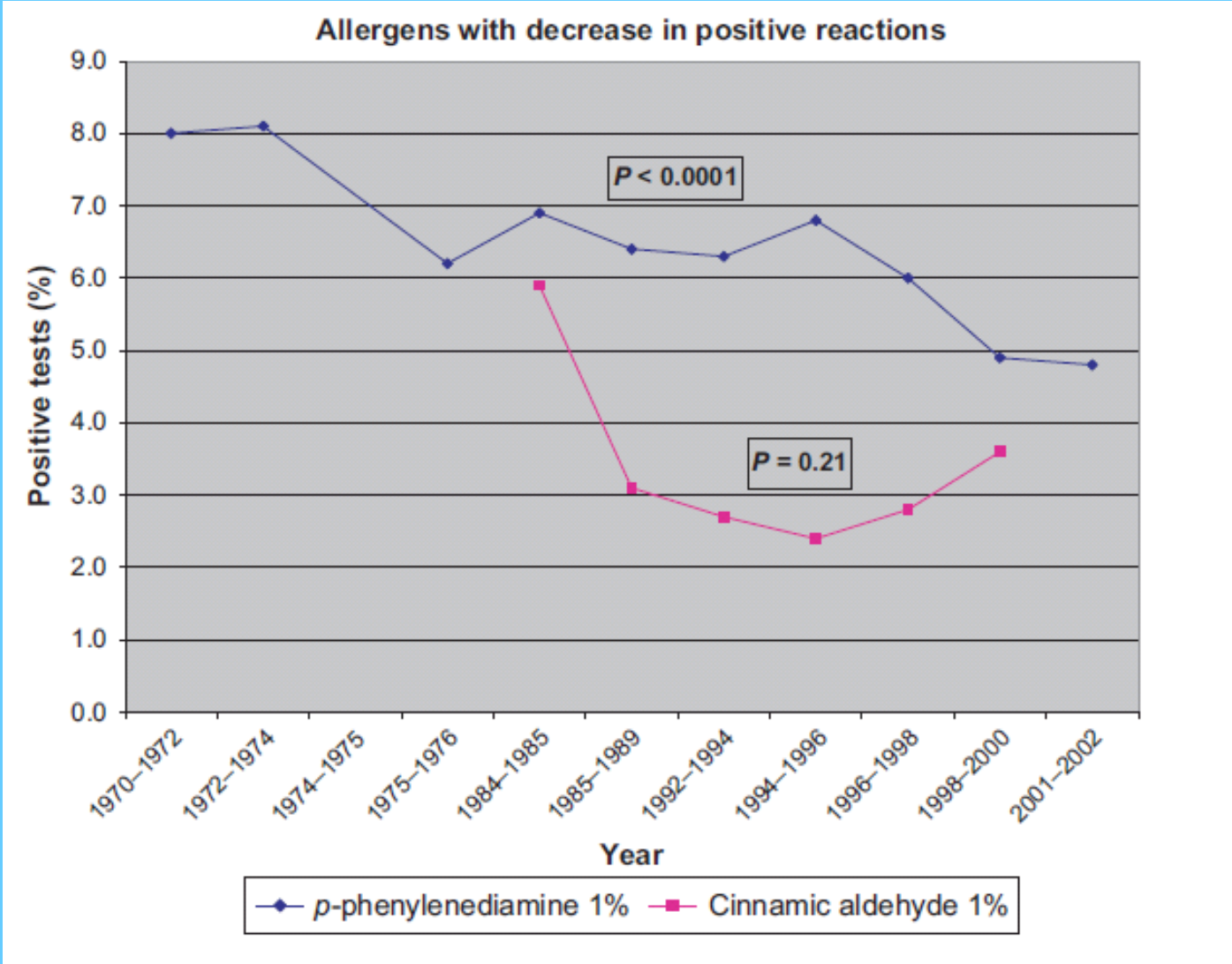
Rubber workers 6%

Sensitization to paraphenylenediamine - international studies

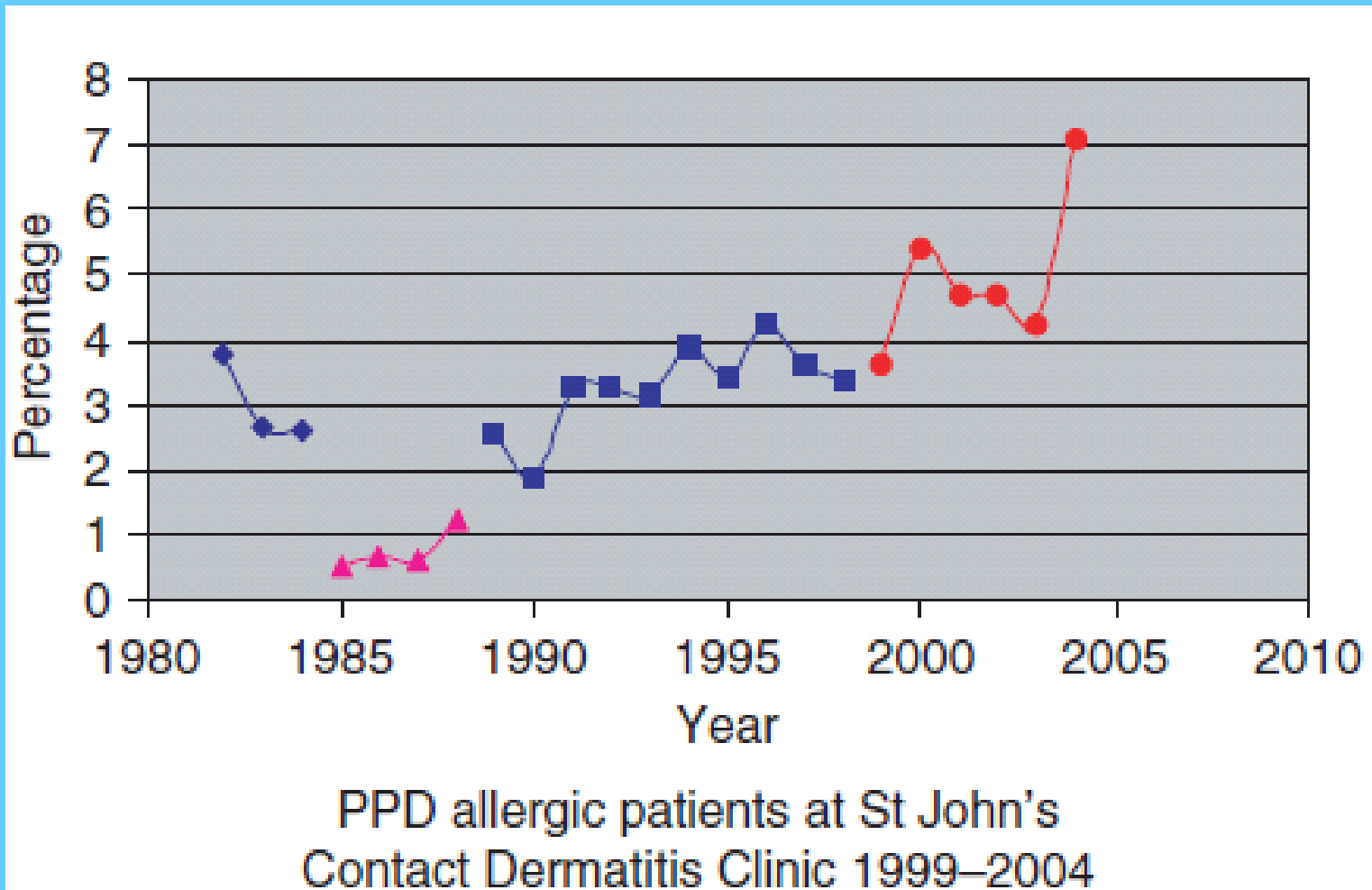
EUROPE

EECDRG	1996– 2000	–	Bruynzeel 2005	3.9%
EECDRG	2003 – 2007	–	Thyssen 2009	4.6%
ESSCA	2002/ 2003	–	Uter 2005	3.1%
ESSCA	2004	–	Writing group 2008	4.1%
ESSCA	2005/ 2006	–	Uter 2009	3.8%

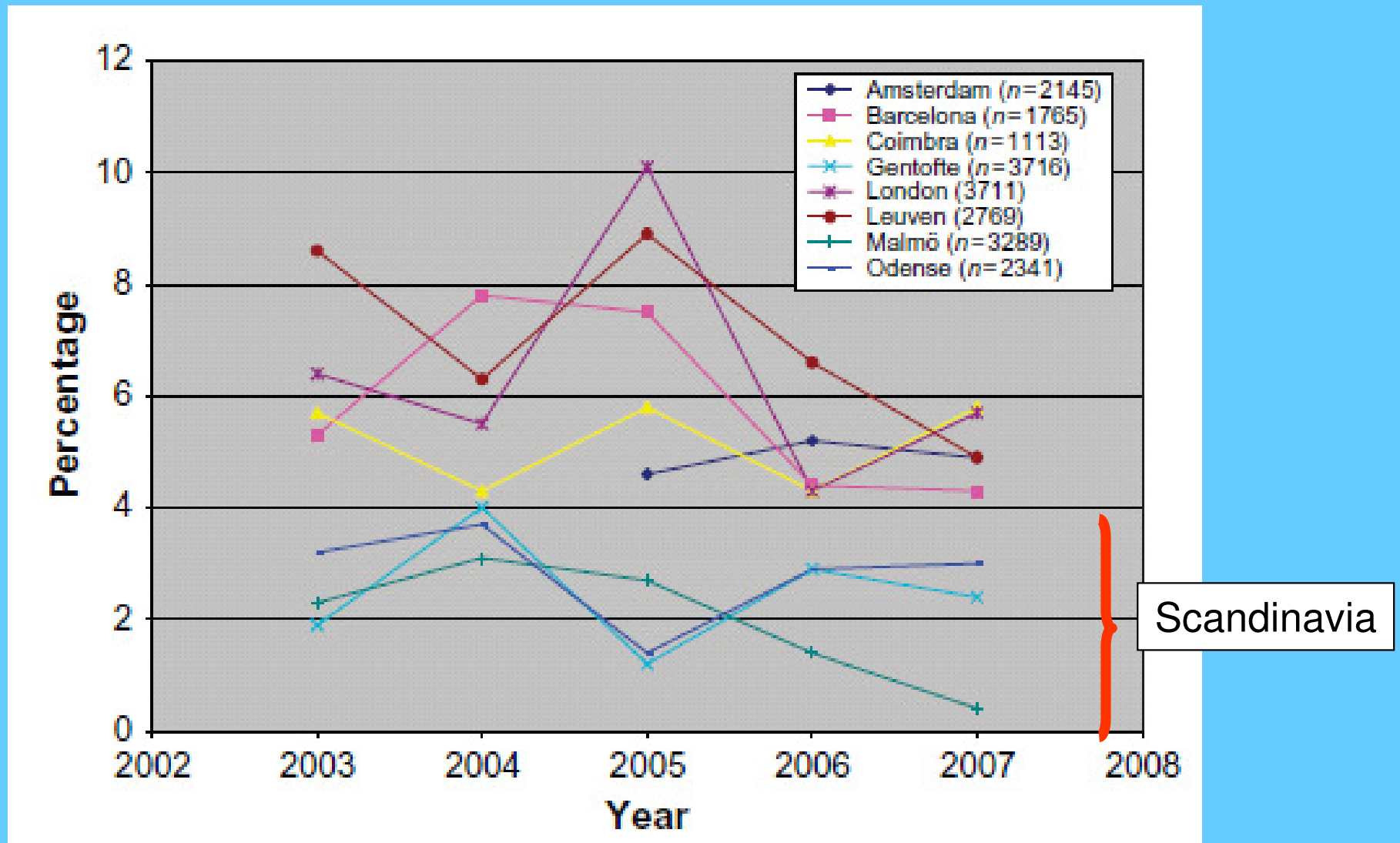
NACDG 1970 - 2002



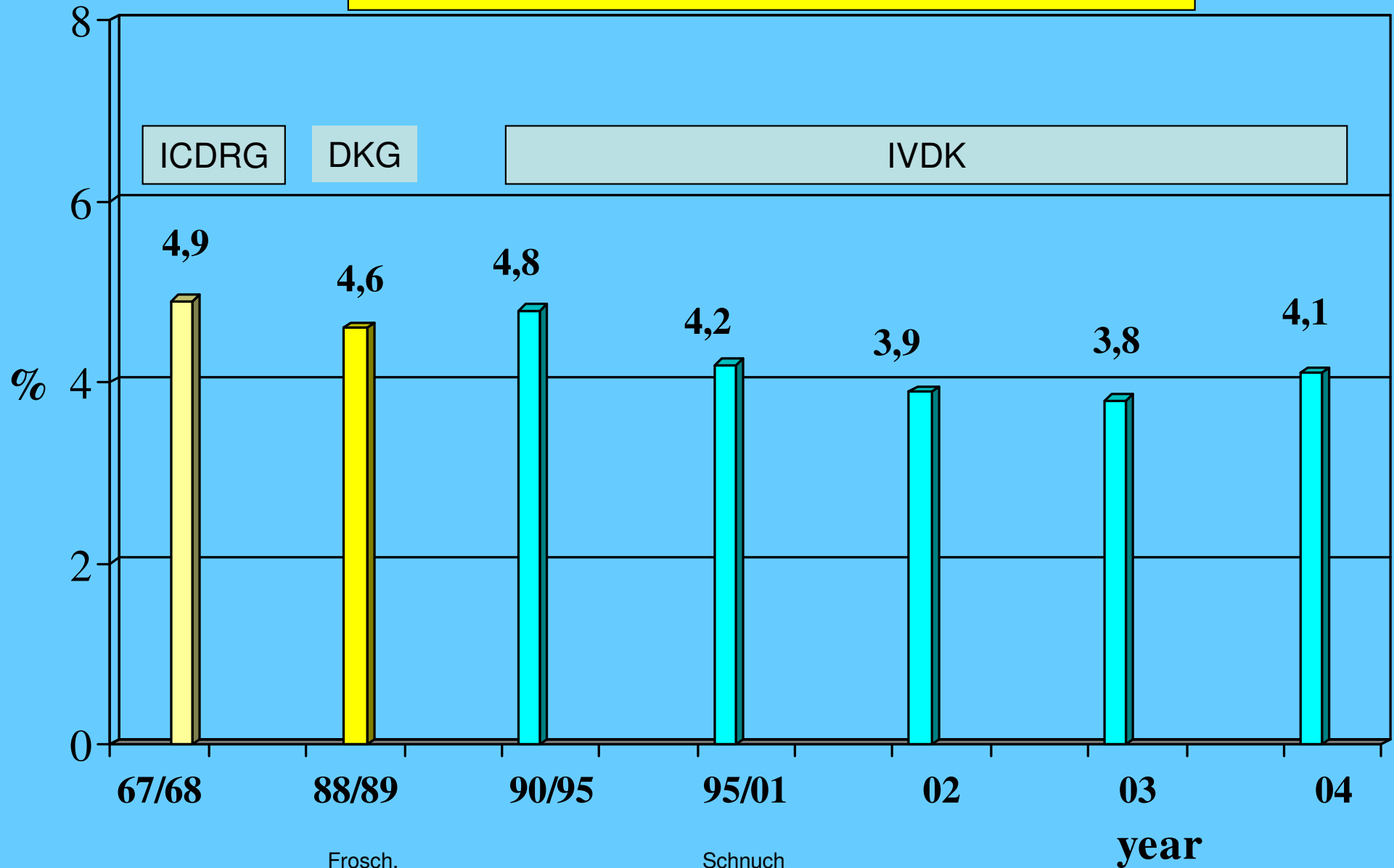
UK (St. John's)



PPD sensitization in Europe: Scandinavian versus central/southern centres



Sensitization to *p*-phenylenediamine - IVDK



Frosch,
Hautarzt 41 (1990)
(Suppl 10): 129

Schnuch
Allergo J,
13 : 57 (2004)

Fregert et al.
Transact St.J.Hosp Derm Soc
55:17 (1969)

Schnuch
Contact Dermatitis
37:200 (1997)

Sensitization to *p*-phenylenediamine - international studies and IVDK

Conclusion

1. Prevalence in Europe

3% – 5%

2. Large geographical differences !

(EECDRG and ESSCA)

Epidemiology

„Traditional“

„Clinical“

„population-based“

population of patients

„The study of the distribution and **determinants** of health-related states or events in specified populations“
(JM Last „A dictionary of epidemiology“ (3rd ed 1995))

What are the determinants of sensitization to PPD

The determinants:

Thyssen et al (2009)

Contact Dermatitis 2009; 60: 314-319
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CONTACT DERMATITIS

***p*-Phenylenediamine sensitization is more prevalent in central and southern European patch test centres than in Scandinavian: results from a multicentre study**

JACOB PONTOPPIDAN THYSSSEN¹, KLAUS EJNER ANDERSEN², MAGNUS BRUZE³, THOMAS DIEPGEN⁴, ANA M. GIMÉNEZ-ARNAU⁵, MARGARIDA GONÇALO⁶, AN GOOSSENS⁷, CHRISTOPHE LE COZ⁸, JOHN MCFADDEN⁹, THOMAS RUSTEMEYER¹⁰, IAN R. WHITE⁹, JONATHAN M. WHITE⁹ AND JEANNE DUUS JOHANSEN¹

Schnuch et al (2008)

CONTACT DERMATITIS AND ALLERGY

BJD British Journal of Dermatology

***para*-Phenylenediamine: the profile of an important allergen. Results of the IVDK¹**

A. Schnuch, H. Lessmann, P.J. Frosch* and W. Uter†

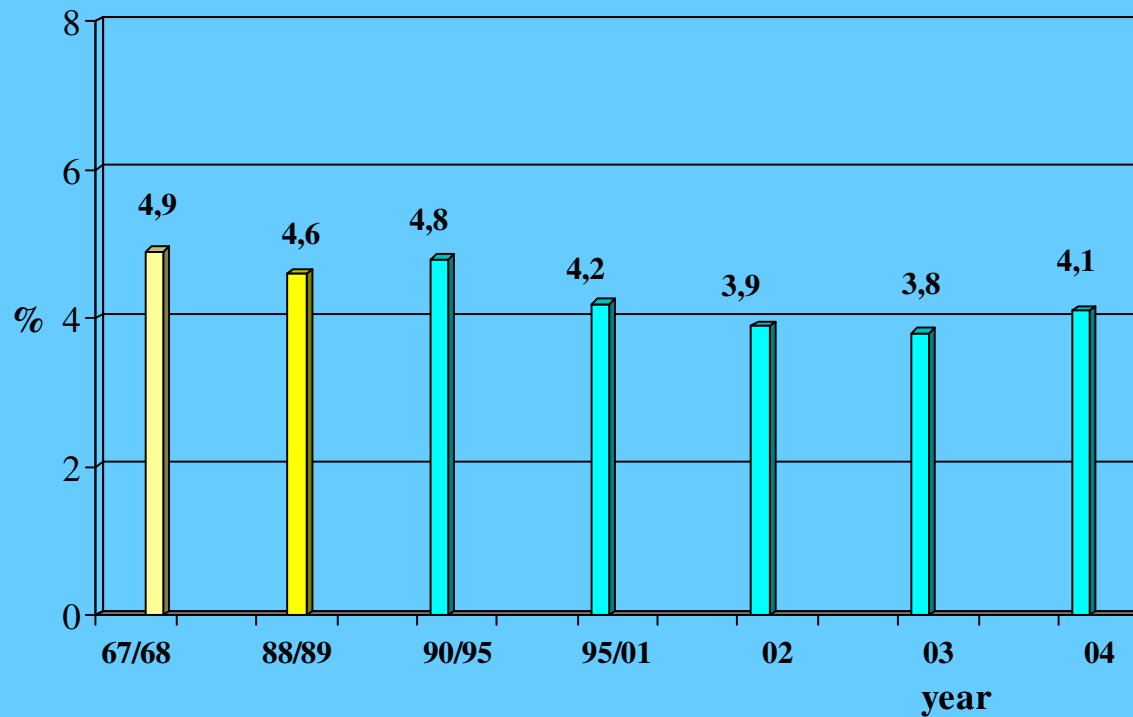
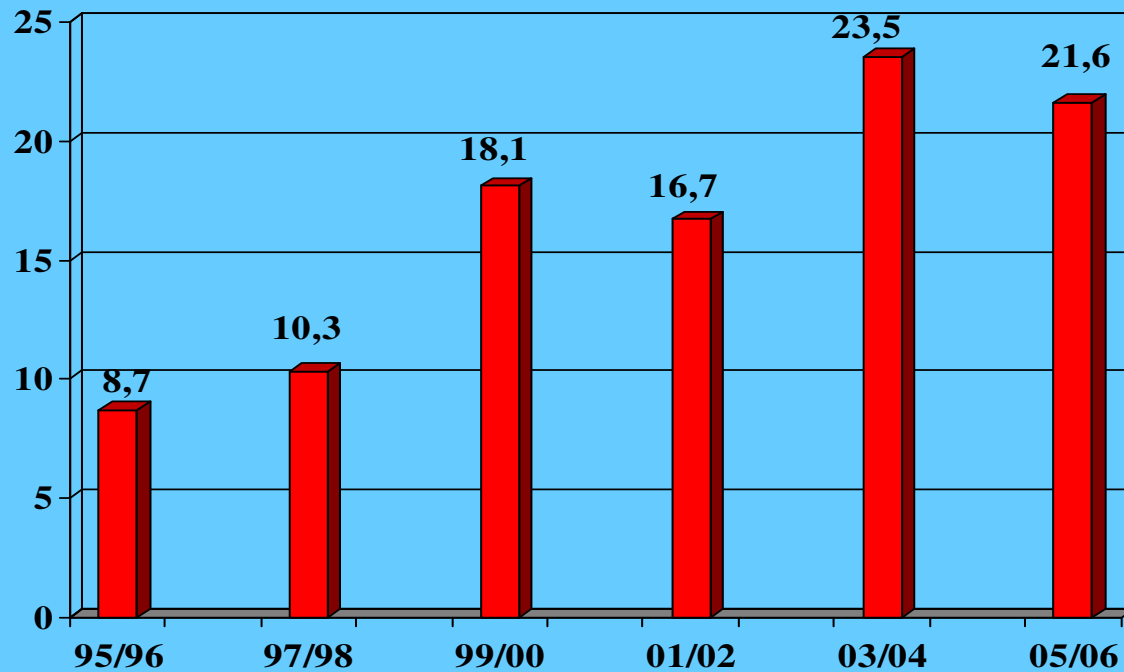
The determinants of sensitization to PPD:

Mainly hair dyes ? Or additional determinants?

Arguments from

a) Epidemiology

b) Patient characteristics (MOAHLFA)



1. Epidemiology:

The significant increase of sensitization to hair dye-related compounds

is not reflected in the trend of PPD over many years

MOAHLFA PPD – positives versus controls (IVDK)

	index	N case	% case	N (Rest)	% (Rest)
Men	M	1154	32.80	30102	37.41
Occup derm	O	845	24.02	11393	14.16
Atop. Dermatitis	A	569	16.17	13766	17.11
Hand-Dermatitis	H	1198	34.05	22143	27.52
leg-Dermatitis	L	408	11.60	8662	10.76
Face-Dermatitis	F	464	13.19	11679	14.51
Age ≥ 40 Jahre	A	2330	66.23	50216	62.40

UK (St. John's) Armstrong 1999: Face Dermatitis: **27%**

The determinants of sensitization to PPD:

Mainly hair dyes ? Or additional determinants?

Arguments from

c) causal exposure / relevance

Causal exposure / Relevance I

Thyssen et al 2009

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CONTACT DERMATITIS

***p*-Phenylenediamine sensitization is more prevalent in central and southern European patch test centres than in Scandinavian: results from a multicentre study**

JACOB PONTOPPIDAN THYSSEN¹, KLAUS EJNER ANDERSEN², MAGNUS BRUZE³, THOMAS DIEPGEN⁴, ANA M. GIMÉNEZ-ARNAU⁵, MARGARIDA GONÇALO⁶, AN GOOSSENS⁷, CHRISTOPHE LE COZ⁸, JOHN MCFADDEN⁹, THOMAS RUSTEMEYER¹⁰, IAN R. WHITE⁹, JONATHAN M. WHITE⁹ AND JEANNE DUUS JOHANSEN¹

n= 21,515

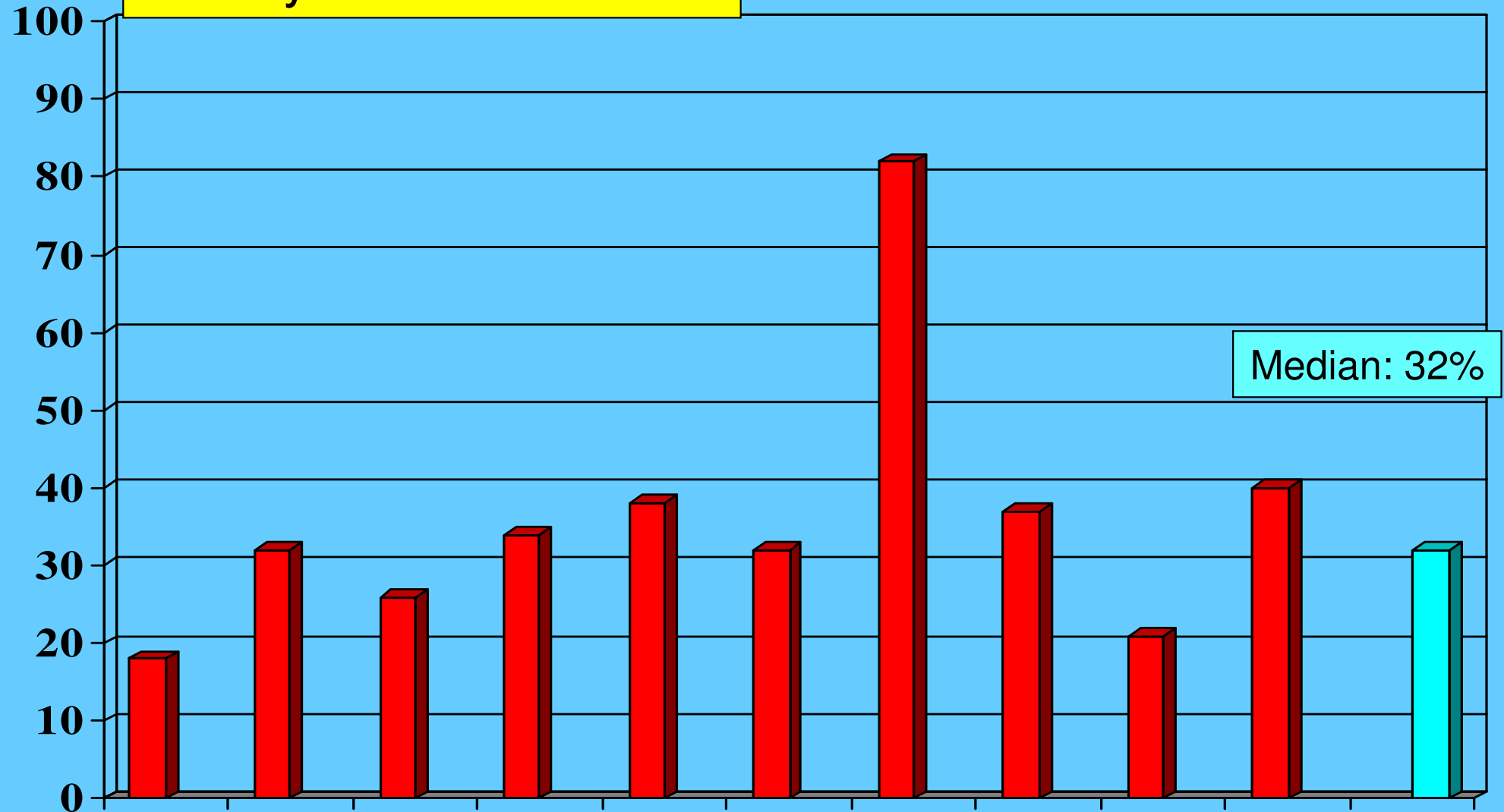
Prevalence: 4.6% (range: 2.1 – 7.1)

Relevance (weighted average)

current	53.6	(range: 17.9 – 70.0)
past	20.3	(range: 0 – 40.0)
unknown	21.9	(range: 6.9 – 61.9)

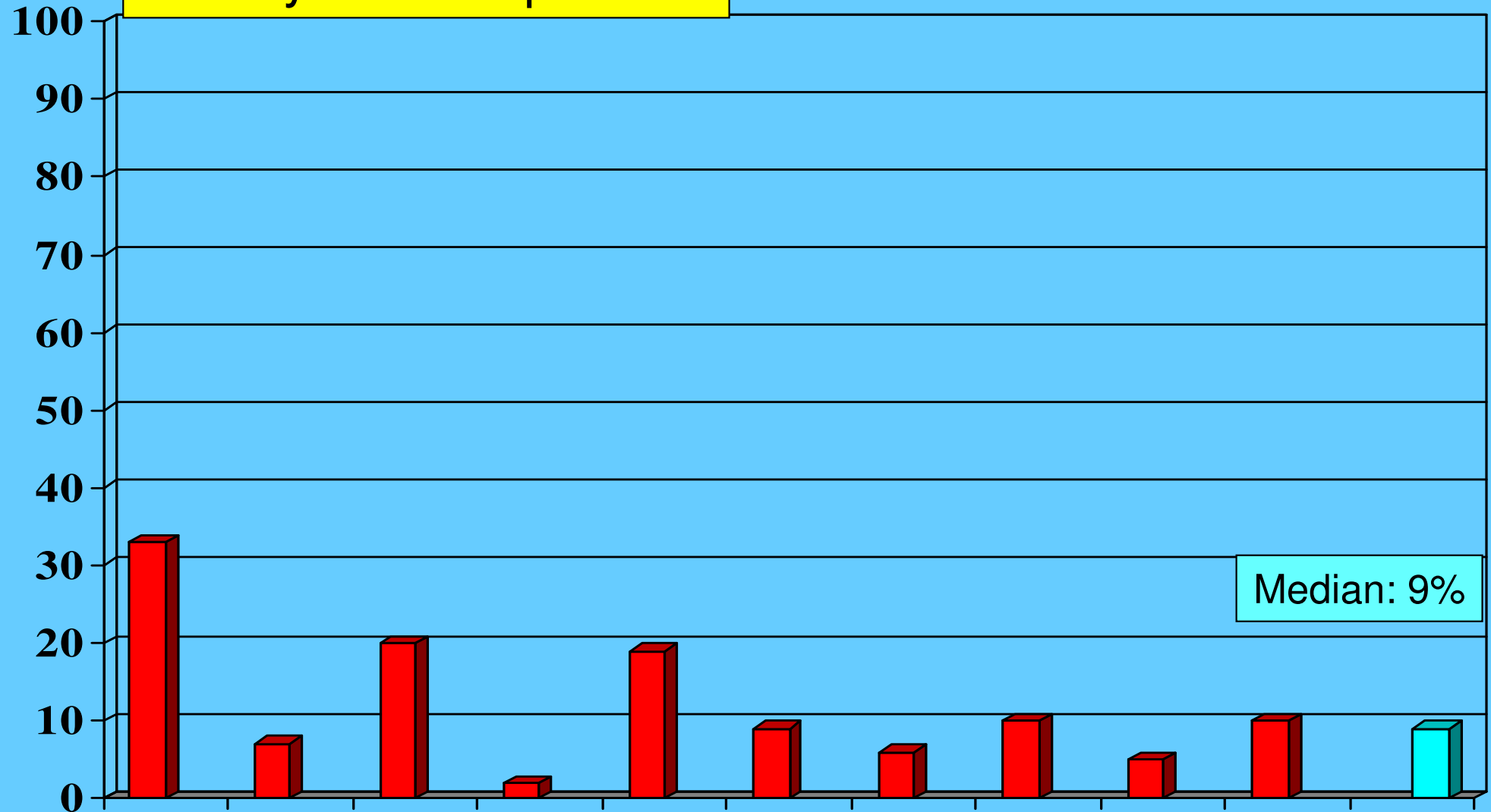
Relevant exposures (%) among **PPD-positive patients**
(Thyssen et al 2009)

Hair dyes / CONSUMER

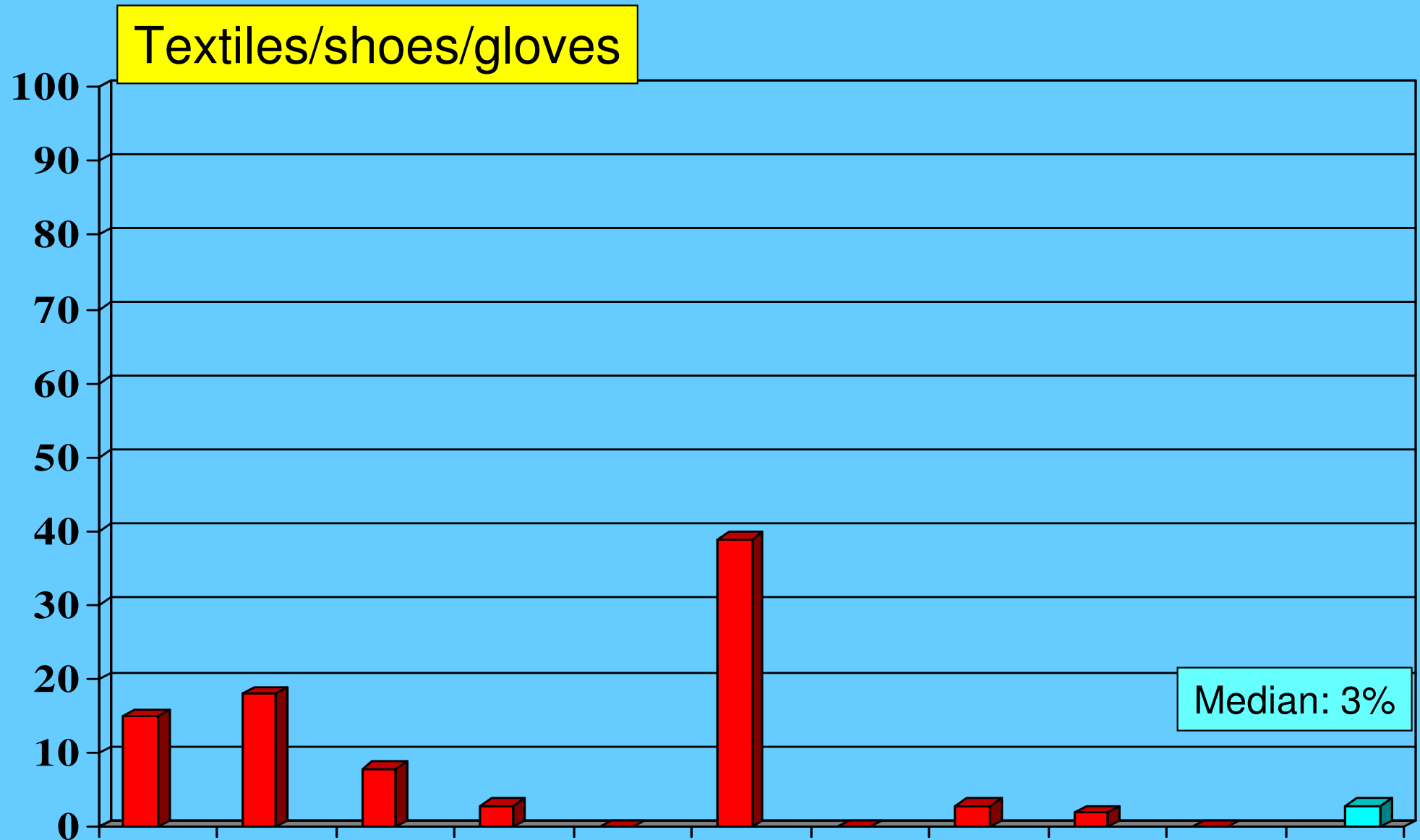


Relevant exposures (%) among **PPD-positive patients**
(Thyssen et al 2009)

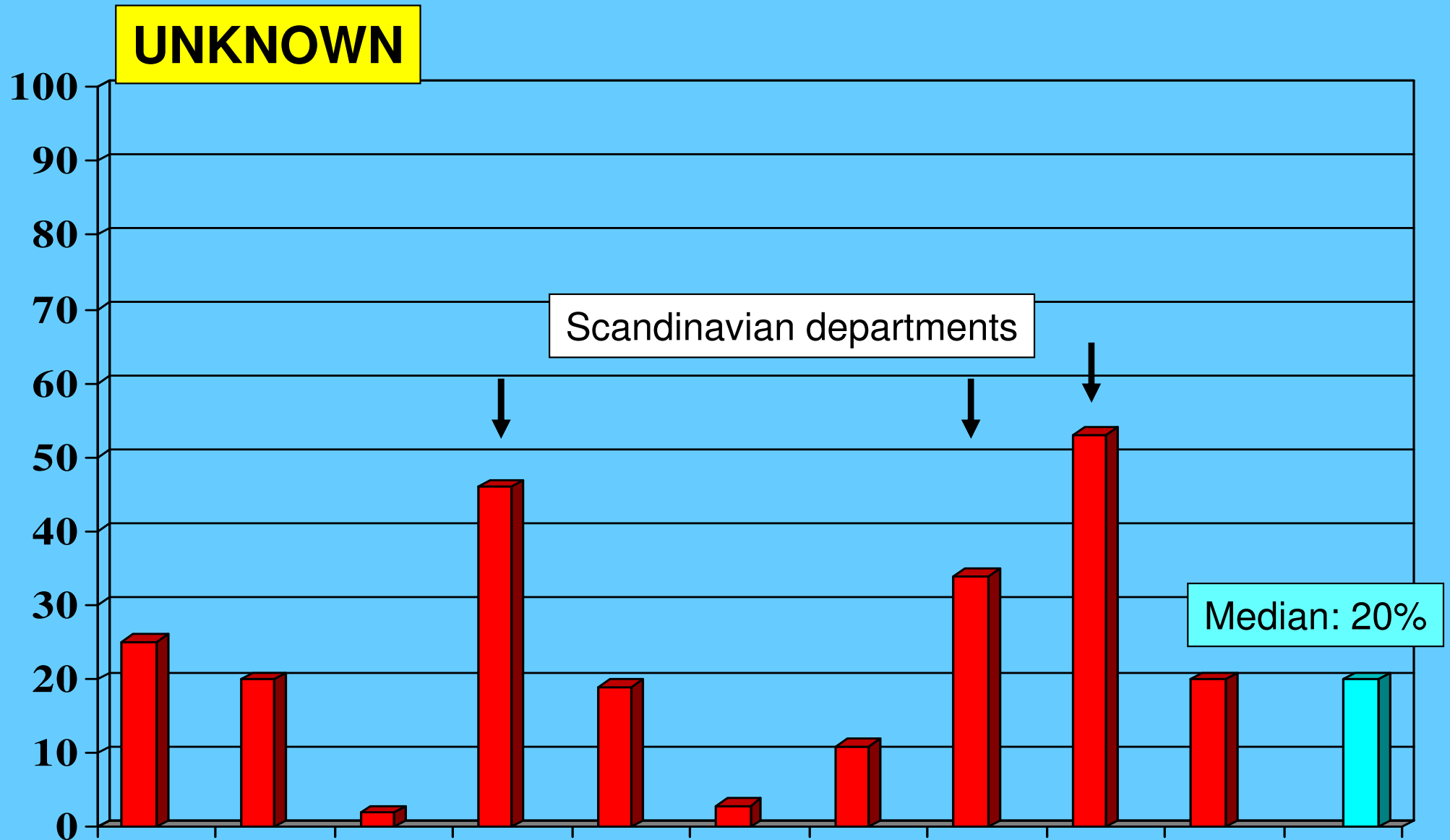
Hair dyes / occupational



Relevant exposures (%) among **PPD-positive patients**
(Thyssen et al 2009)



Relevant exposures (%) among PPD-positive patients (Thyssen et al 2009)



Causal exposure / Relevance II

Schnuch et al 2008

CONTACT DERMATITIS AND ALLERGY

BJD British Journal of Dermatology

***para*-Phenylenediamine: the profile of an important allergen. Results of the IVDK¹**

A. Schnuch, H. Lessmann, P.J. Frosch* and W. Uter†

The cause of PPD Allergy ?

Registered data

assumed exposure

Face/head +
(Hand/ occup. -)



Hair dyeing

Textiles, gloves
shoes +



„Textiles“

Occupational cause +
Hands +



Occupation

unresolved rest

Fractionation of PPD allergy

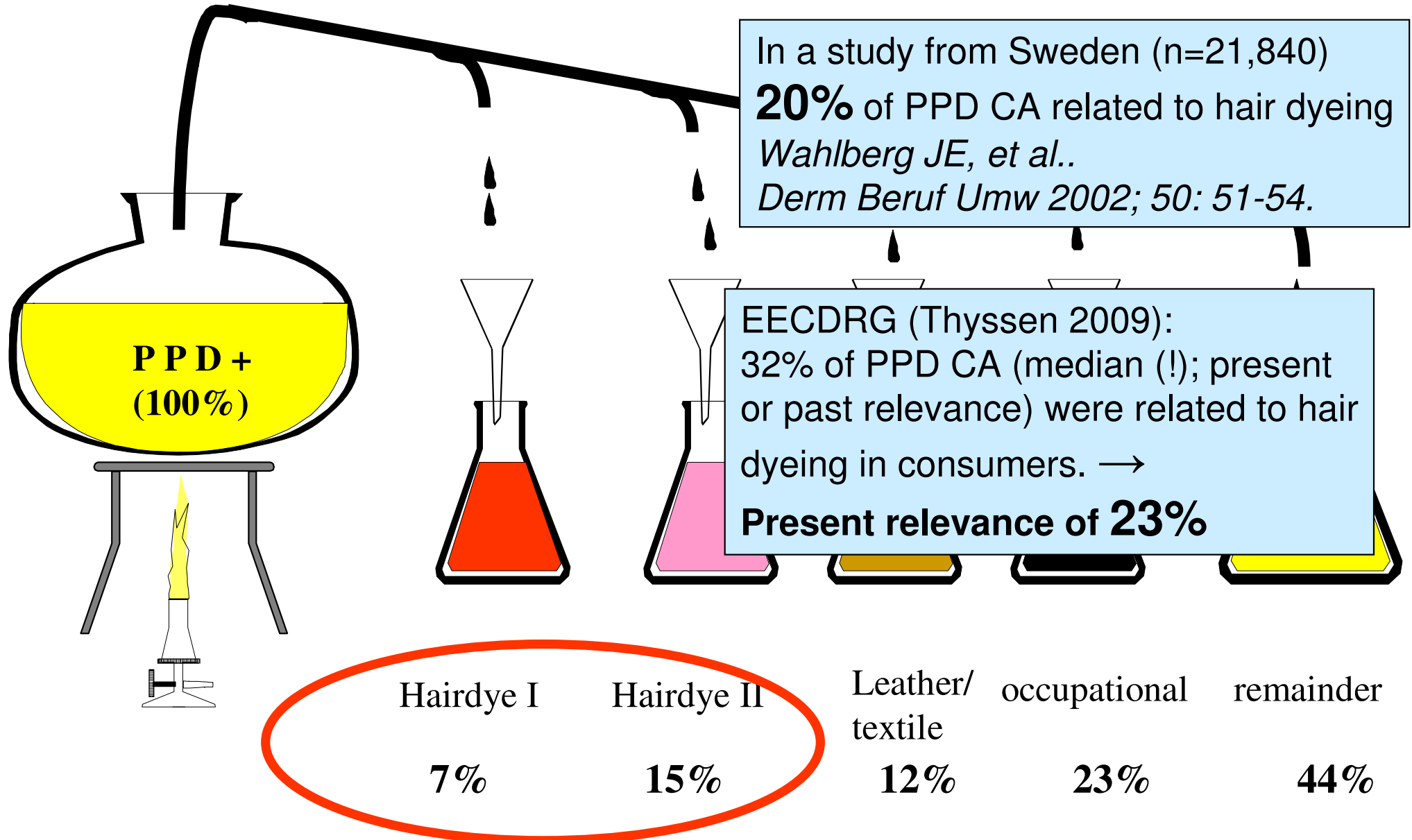
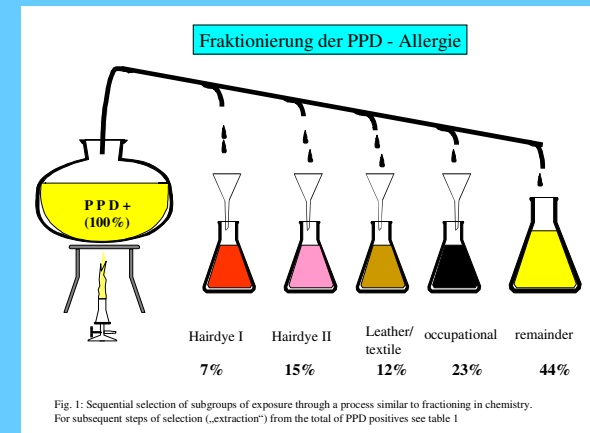


Fig. 1: Sequential selection of subgroups of exposure through a process similar to fractionation in chemistry. For subsequent steps of selection („extraction“) from the total of PPD positives see table 1

The cause of PPD Allergy ?



„Fractioning“ (Allocation to subgroups) was confirmed:

a) Concomitant sensitization (= marker for exposure)

b) Regression analysis

a) Concomitant reactions in PPD positives

	Hairdye I			Hairdye II			Leather/textile			Occupat			Rest		
Allergen	% (pos.)std.	95%	KI	% (pos.)std.	95%	KI	% (pos.)std.	95%	KI	% (pos.)std.	95%	KI	% (pos.)std.	95%	KI
p-Toluyldiamin (freie Base)	76.56	69.62	83.49	51.38	39.11	63.65	38.72	26.02	51.42	63.60	56.32	70.89	51.25	42.65	59.85
p-Aminophenol (CI 76550)	45.14	35.92	54.35	30.35	18.48	42.23	9.92	4.02	15.81	18.61	12.63	24.59	22.83	4.30	41.36
3-Aminophenol	30.99	22.72	39.27	22.06	10.65	33.47	11.67	0.00	23.41	13.23	6.05	20.41	4.43	0.00	9.20
Other PARA															
p-Aminoazobenzol (CI 11000)	58.31	47.04	69.58	68.16	54.10	82.22	58.96	50.22	67.69	64.11	55.94	72.27	60.38	52.34	68.41
4,4'-Diaminodiphenylmethan	51.35	35.59	67.12	35.78	21.54	50.02	30.63	21.83	39.42	28.93	22.14	35.73	30.98	24.33	37.62
Dispers Orange 3 (CI 11005)	40.97	27.69	54.26	46.90	35.88	57.93	31.68	23.19	40.18	40.70	31.60	49.79	45.34	34.71	55.98
Benzocain (Ethylaminobenzoat)	21.44	13.83	29.06	13.20	9.66	16.75	9.83	6.96	12.71	12.88	10.41	15.35	19.34	17.13	21.54
N-Isopropyl-N'-phenyl-p-phenylendiamin	11.87	5.85	17.90	5.92	3.11	8.73	9.07	6.35	11.79	8.01	6.13	9.89	6.71	5.03	8.39
N,N'-Diphenyl-p-phenylendiamin (DPPD)	0.00	0.00	0.00	1.94	0.00	5.76	5.51	2.34	8.67	9.08	5.89	12.27	3.70	1.00	6.39
Occupation/textile/leather															
Ammoniumpersulfat	3.52	1.38	5.66	8.77	3.82	13.72	17.45	5.24	29.66	35.27	27.28	43.27	25.00	5.63	44.37
Glycerylmonothioglykolat	1.82	0.23	3.41	5.35	1.19	9.51	16.42	2.68	30.15	29.16	19.89	38.43	12.60	0.00	25.25
Kaliumdichromat	3.75	0.02	7.48	5.34	3.20	7.47	15.44	11.90	18.97	12.23	9.79	14.68	10.87	8.96	12.77
Dibromdicyanobutan + 2-Phenoxyethanol	3.05	0.00	7.00	5.18	3.27	7.09	5.85	3.55	8.15	8.29	6.21	10.37	5.44	4.12	6.77
(Chlor)-Methylisothiazolinon (MCI/MI)	1.53	0.19	2.88	2.52	1.19	3.85	2.68	1.02	4.35	8.15	6.09	10.21	4.20	2.99	5.40
Kolophonium	2.57	0.81	4.34	7.86	5.25	10.46	9.94	7.00	12.89	8.05	6.04	10.07	8.05	6.46	9.65
Thiuram Mix	7.94	1.75	14.14	2.07	0.84	3.30	14.05	10.56	17.54	7.04	5.18	8.90	5.86	4.44	7.27
Formaldehyd	2.66	0.00	6.24	3.87	1.92	5.83	5.78	3.50	8.06	4.04	2.57	5.51	2.69	1.74	3.64
Epoxidharz	0.28	0.00	0.82	2.82	0.66	4.99	1.88	0.59	3.17	3.66	2.29	5.03	2.34	1.40	3.28
p-tert.-Butylphenol-Formaldehydharz	0.62	0.00	1.50	3.70	1.39	6.00	2.89	1.18	4.59	3.13	1.87	4.39	3.42	2.27	4.57
Mercapto-Mix ohne MBT)	0.36	0.00	1.07	0.26	0.00	0.61	5.82	3.47	8.17	2.34	1.22	3.45	3.03	1.87	4.19

a) Concomitant reactions in PPD positives

	Hairdye I	II	Leather/ textile	Occupat	Rest
Allergen	%	%	%	%	%
p-Toluyldiamin	76.56	51.38	38.72	63.60	51.25
p-Aminophenol	45.14	30.35	9.92	18.61	22.83
3-Aminophenol	30.99	22.06	11.67	13.23	4.43

a) Concomitant reactions in PPD positives

Allergen	Hairdye I II		Leather/ textile	Occupat	Rest
	%	%	%	%	%
Potassium dichromat	3.75	5.34	15.44	12.23	10.87
Kolophonium	2.57	7.86	9.94	8.05	8.05
Thiuram Mix	7.94	2.07	14.05	7.04	5.86
Formaldehyd	2.66	3.87	5.78	4.04	2.69
Mercapto-Mix (without MBT)	0.36	0.26	5.82	2.34	3.03

a) Concomitant reactions in PPD positives

Hairdye I II Leather/ Occupat Rest
textile

Allergen	%	%	%	%	%
p-Toluylenediamine	76.56	51.38	38.72	63.60	51.25
Occupational allergens					
Ammoniumpersulfat	3.52	8.77	17.45	35.27	25.00
Glycerylmonothioglykolat	1.82	5.35	16.42	29.16	12.60
Potassiumdichromat	3.75	5.34	15.44	12.23	10.87
Dibromdicyanobutan + 2-Phenoxyethanol	3.05	5.18	5.85	8.29	5.44
(Chlor)-Methylisothiazolinon (MCI/MI)	1.53	2.52	2.68	8.15	4.20
Colophony	2.57	7.86	9.94	8.05	8.05
Thiuram Mix	7.94	2.07	14.05	7.04	5.86
Epoxy resin	0.28	2.82	1.88	3.66	2.34
p-tert.-Butylphenol-Formaldehyde resin	0.62	3.70	2.89	3.13	3.42

b) Regression analysis

Independent risk factors (**significant**):

Female	1.15
Face etc.	1.39
Hands	1.26
Occupational cause	2.14

Hairdressers !	3.24
Construction workers	1.52
agriculture	1.33
Textile worker, painter, printer	>1 (n.s.)

} **IPPD**
(Rubber)

The cause of PPD Allergy ?

Unresolved Rest:

- Age ↑
- Site of eczema: Leg ↑
- concomitant sensitization: unspecific

No hint for a specific exposure

The cause of PPD Allergy ?

Unresolved Rest – Possible explanations:

„historical“ Sensitization / past relevance?

active sensitization through testing PPD ?

Active sensitization to PPD

Skog E. Sensitization to p-phenylenediamine. 1965

Calnan CD. Studies in contact dermatitis (XX). Active sensitization. 1967

Cronin E. Contact Dermatitis. 1980

Foussereau J. Les eczémas allergiques...1987

Devos SA, van-der-Valk PGM. The risk of active sensitization to PPD. 2001

Hillen U, et al. Late reactions to... PPD (and retesting) 2006

Aalto-Korte K et al Late reactions in patch tests (and retesting)... 2007

The quantitative dimension:

~ 1/4 of the PPD allergics might be sensitized through patch testing with PPD 1%;
i.e. the patch test may be an important source of sensitization

[Hillen et al (2006); Aalto-Korte et al (2007)]

Alternative position summarized by Gawkrödger and English, BJD 154:1025 (2006)

Aalto-Korte K et al: „ Our high level of active sensitization to PPD is unacceptable, considering our low number of relevant PPD reactions“

The determinants of sensitization to PPD:

Arguments from

c) Causal exposure / Relevance

Relevance from patients history

Individual relevance

- relies on the knowledge of
the patient
the dermatologist
- assessment not standardized !!
- quality may vary

Relevance from clinical epidemiology

Epidemiologic relevance

- relies on the knowledge of
the patient
the dermatologist
- clinical data and their associations
- statistical significance

The determinants of sensitization to PPD:

Mainly hair dyes ? Yes,
through occupational and non-occupational exposure,
but additional determinants should be considered

The frequency of sensitization to PPD

In the **general population**

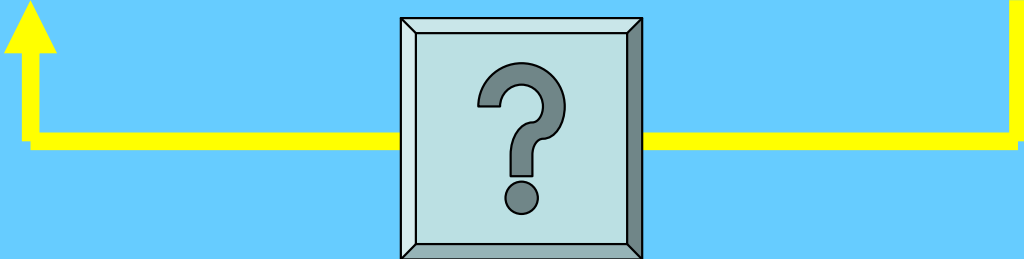
The CE - DUR approach

Epidemiology

„Traditional“
general population



„Clinical“
population of patients



Drug Utilization Research (DUR)

among others, to estimate morbidity:

The number of diseased persons is calculated based on specific drug consumption...

....namely, of drugs exclusively !
used to treat one single disease

- anticonvulsants → epidemiology of **epilepsy** (*J Clin Epidem.* 50:1061 (1997))
- Adrenalin → epidemiology of **anaphylaxis** (*JACI* 110:547 (2002))

....and also diagnostics exclusively used for one purpose,
e.g. **patch test** to diagnose **allergic contact dermatitis**

Epidemiology

„Traditional“

general population



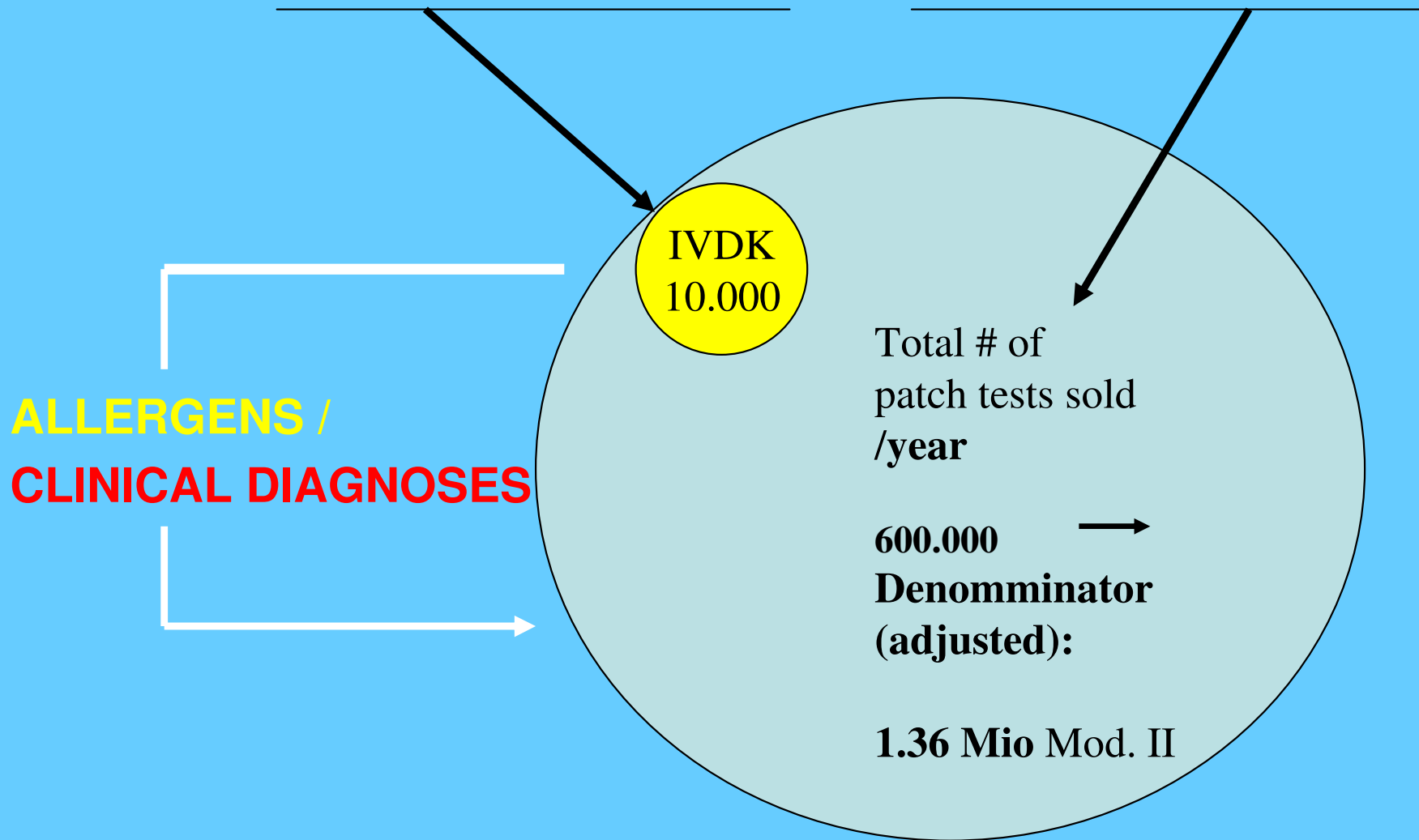
„Clinical“

population of patients



Patch test sold

CE-DUR: Clinical Epidemiology – Drug Utilization Research



CE-DUR: VALIDITY OF THE MODEL II

Thyssen et al (BJD; 2009): Fragrance allergy in the general population

prevalence of sensitization to FM I **1.6%** (95% CI: 1.2-2.1%)

CE-DUR model III	1.0%
CE-DUR model I	2.4%

Prevalence of sensitization to PPD
in the general population:

0.5% - 1.2%

Hair dye related PPD sensitization
in the general population:

0.1% - 0.2%

According to a „medium“ and „worst case“ scenario of the CE-DUR model

INCIDENCE

Of hair dye related PPD sensitization

in the population regularly dyeing hairs

(~ 15 Mio)

6 / 1000 / year

Ende