General Hazard Profile of Pigments

First International Conference on Tattoo Safety
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Dr. W. Teubner, EUROTOX-registered toxicologist

Product Safety Switzerland

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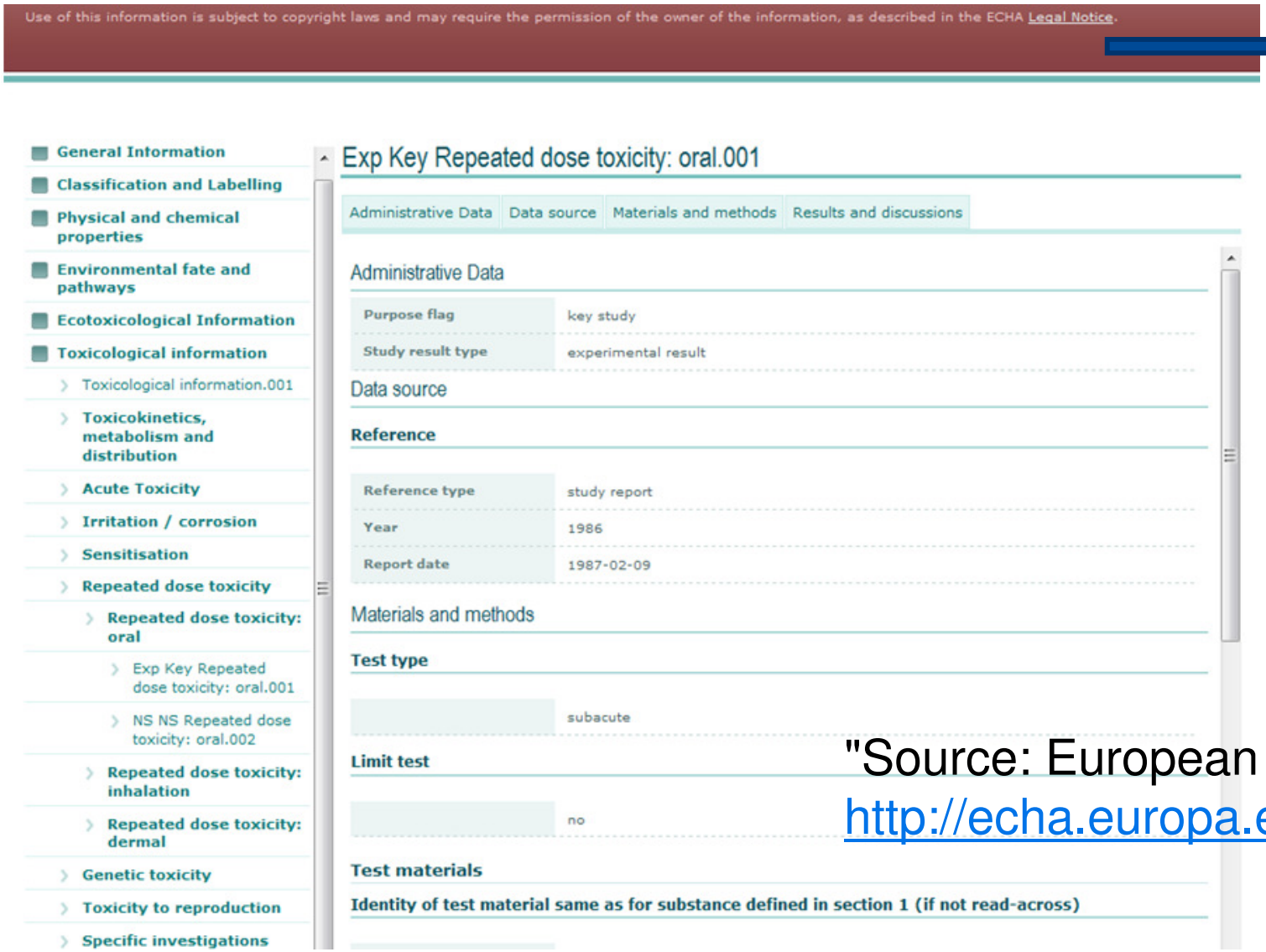
The Chemical Company

A note at the beginning…

- Data presented on the following slides
  - has been gathered for the purposes of registration as an industrial chemical in the EU
  - can be viewed online in form of robust study summaries at the European Chemicals Agency (ECHA)
- BASF markets pigments for industrial uses (eg coating of cars, coloration of plastic articles, printing inks)
- BASF does not support uses in tattoo inks

Disseminated data via the European Chemicals Agency



Note
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"Source: European Chemicals Agency, http://echa.europa.eu/".

Key points of EC regulation 1907/2006 (REACH)

- Registrants share available company data
  - Study reports are reviewed for adequacy and reliability
  - Legal agreements (letter of access, etc)
- Hazard data from public databases is gathered
  - Literure data are reviewed for adequacy and reliability
  - Newly identified data holders are contacted for data sharing

Data gap filling with studies performed under GLP and following OECD testing guidelines

(deviations from standard procedure as in Annex XI)

Data base for industrial pigments

- Representative of pigments alone, not of pigment formulations (dispersing agents, fillers, etc)
- Thourough literature survey
- Experimental data from stakeholders interested in REACH
  - Companies with volumes of more than 1 tpa and active in the EU
  - Otherwise interested (data owners)
- No completeness claimed - possible existence of further experimental data for non-industrial uses or data held by stakeholders outside the EU

Data sources, examples Pigment Red 254, Pigment Red 101

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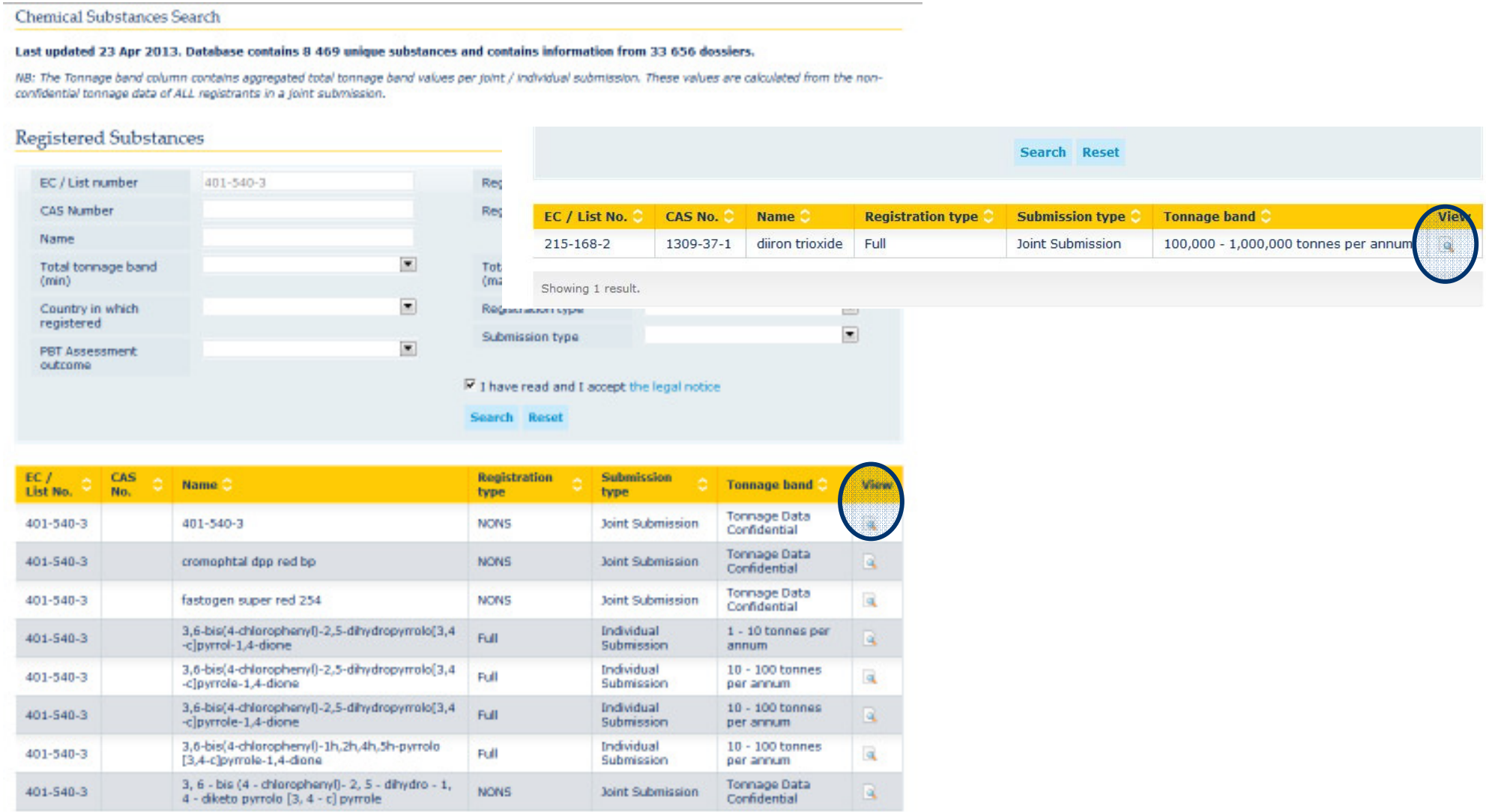

Chemical Substances Search

Last updated 23 Apr 2013. Database contains 8 469 unique substances and contains information from 33 656 dossiers.

NB: The Tonnage band column contains aggregated total tonnage band values per joint / individual submission. These values are calculated from the non-confidential tonnage data of ALL registrants in a joint submission.

Registered Substances

EC / List number: 401-540-3
CAS Number:
Name:
Total tonnage band (min):
Country in which registered:
PBT Assessment outcome:
Submission type:
I have read and I accept the legal notice
Search Reset

Search Reset

EC / List No.	CAS No.	Name	Registration type	Submission type	Tonnage band	View
215-168-2	1309-37-1	diiron trioxide	Full	Joint Submission	100,000 - 1,000,000 tonnes per annum	

Showing 1 result.

EC / List No.	CAS No.	Name	Registration type	Submission type	Tonnage band	View
401-540-3		401-540-3	NONS	Joint Submission	Tonnage Data Confidential	
401-540-3		cromophtal dpp red bp	NONS	Joint Submission	Tonnage Data Confidential	
401-540-3		fastogen super red 254	NONS	Joint Submission	Tonnage Data Confidential	
401-540-3		3,6-bis(4-chlorophenyl)-2,5-dihydropyrrolo[3,4-c]pyrrol-1,4-dione	Full	Individual Submission	1 - 10 tonnes per annum	
401-540-3		3,6-bis(4-chlorophenyl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione	Full	Individual Submission	10 - 100 tonnes per annum	
401-540-3		3,6-bis(4-chlorophenyl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione	Full	Individual Submission	10 - 100 tonnes per annum	
401-540-3		3,6-bis(4-chlorophenyl)-1h,2h,4h,5h-pyrrolo [3,4-c]pyrrole-1,4-dione	Full	Individual Submission	10 - 100 tonnes per annum	
401-540-3		3, 6 - bis (4 - chlorophenyl)- 2, 5 - dihydro - 1, 4 - diketo pyrrolo [3, 4 - c] pyrrole	NONS	Joint Submission	Tonnage Data Confidential	

"Source: European Chemicals Agency, http://echa.europa.eu/". May 28th, 2013

Impact of impurities on classification and labelling

exemple from ECHA dissimination view

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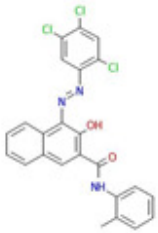
- General Information
  - Identification
  - Compositions
- Classification and Labelling
  - GHS
    - Pigment Red 112 [not classified, < 1% (w/w) Naphtol AS-D, 3-hydroxy-2'-methyl-2-naphthanilide]
    - Pigment Red 112 [classified > 1% (w/w) Naphtol AS-D, 3-hydroxy-2'-methyl-2-naphthanilide]
  - DSD - DPD
- Physical and chemical properties
- Environmental fate and pathways
- Ecotoxicological Information
- Toxicological information
- Guidance on safe use
- Reference substances

Identification

Substance identification

3-hydroxy-N-(o-tolyl)-4-[(2,4,5-trichlorophenyl)azo]naphthalene-2-carboxamide

EC Number	229-440-3
EC Name	3-hydroxy-N-(o-tolyl)-4-[(2,4,5-trichlorophenyl)azo]naphthalene-2-carboxamide
CAS Number	6535-46-2
Molecular formula	C24H16Cl3N3O2
IUPAC Name	3-hydroxy-N-(2-methylphenyl)-4-[(2,4,5-trichlorophenyl)diazenyl]-2-naphthamide



Type of substance

Composition	mono constituent substance
Origin	organic

"Source: European Chemicals Agency, http://echa.europa.eu/". May 28th, 2013

Pigment classes, examples

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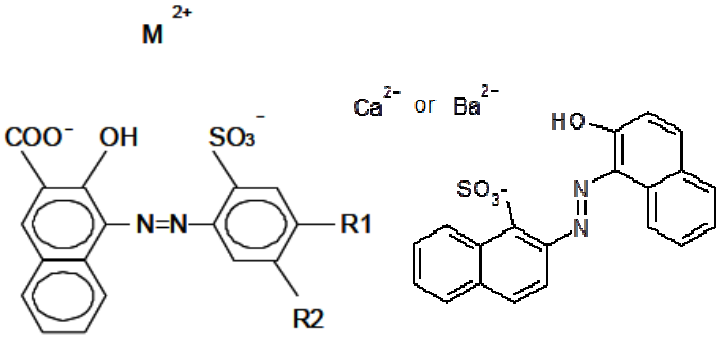
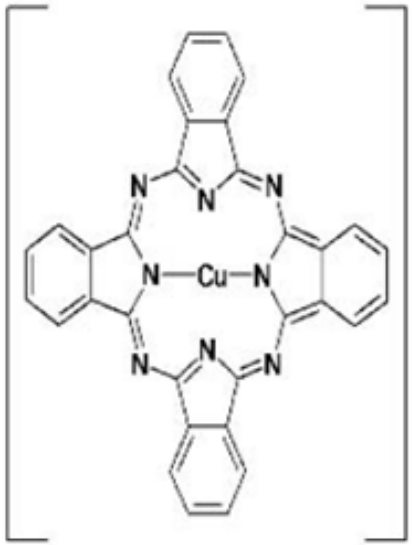
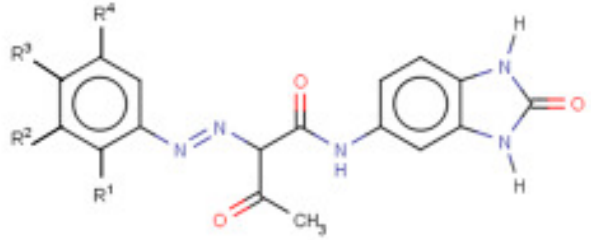


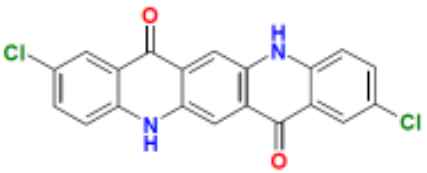
Metal-laked pigments



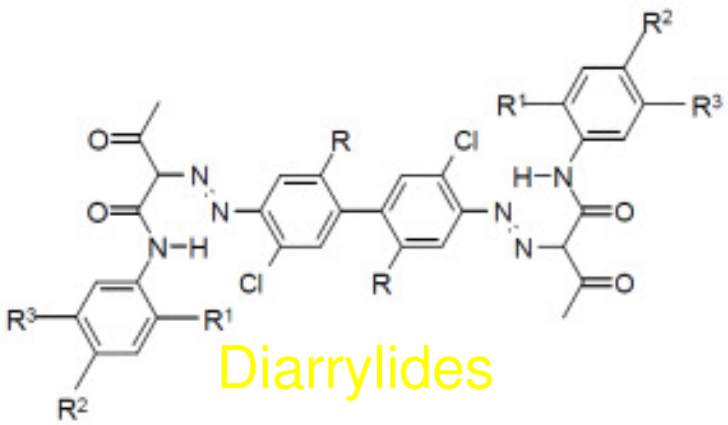
Copper-phthalocyanines



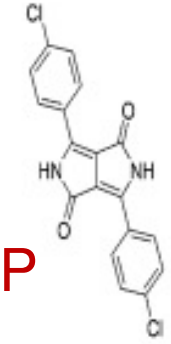
Acetolones



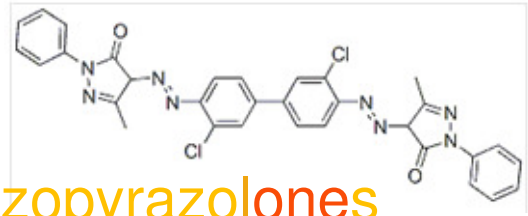
Quinacridones



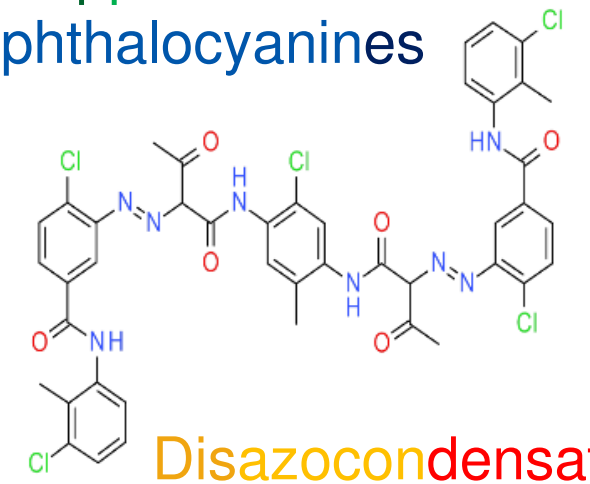
Diarrylides



DPP



Disazopyrazolones



Disazocondensations

Inorganics (Iron oxides, TiO_2)

General physico-chemical properties, organic pigments

- Range of molecular weight: 350 (PR 254) - 1394 (PG 36) g/mol
- Water solubility (neutral pH) range ng – mg/L (methodical challenges)

  Poorly soluble - insoluble

  - some pigments soluble at extreme pH (eg PR 57:1)
- Octanol solubility range ng – mg/L (methodical challenges)
- Relative density > 1

  Poorly soluble - insoluble
- No melting point up to decomposition temperature (200 – 400 °C, actual temperature depending on the pigment)

Mandatory endpoints covered by REACH at maximum tonnage band

- Acute toxicity, relevant routes
- Skin irritation, eye irritation, skin sensitization
- Genotoxicity (bacteria, mammalian cells in vitro, in-vivo if in-vitro testing indicates a hazard)
- Repeated dose toxicity, relevant route
- Reproductive toxicity (Fertility by 2-generation study, developmental toxicity/ teratogenicity study; 2 species), relevant route
- Carcinogenicity, two species, relevant route

Hazard data available for members of all mentioned chemical classes (I)

LD50 (oral) > 2000 mg/kg bw
LD50 (dermal) > 2000 mg/kg bw

virtually non-toxic by ingestion and skin contact

Skin irritation: non irritating

Eye irritation: non irritating

Skin sensitisation: non sensitising

Genotoxicity: not genotoxic (Ames with and without Prival-modification, Hprt/MLA, cytogenetic tests, in-vivo micronucleus, UDS)

Hazard data for members of all chemical classes (II) – Repeated-dose toxicity

Rats, 28-days or 42 days, oral dosing
More than 20 pigments: NOEL = 1000 mg/kg bw

Rats, 90-days, oral dosing
Pigment Yellow 74, Pigment Red 122; Pigment Green 15: NOEL = 1000 mg/kg bw

Metal laked pigments (dissociation in stomach acid):
Adverse effects on kidneys upon bolus dosing, NOEL ca 40 mg/kg bw); red discoloration of urine

18-months dermal toxicity study: PR 57:1 for use in lipstick (Carson 1984); dose 50 mg/kg bw, twice per week

Carson S (1984). Skin Painting Studies in Mice with 14 FD&C and D&C Colors. J. Toxicol. - Cut. and Ocular Toxicol. 3 (4), 357 - 370.

Hazard data for members of all chemical classes (III) Carcinogenicity

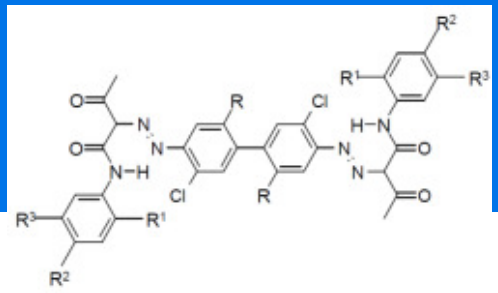
- Na salt of Pigment Red 57:1 (feeding study, non carcinogenic)
- Skin painting «lipstick» studies (Carson 1984)
- Leuschner 1978 - Toxicology Letters 2: 253-260 (diarrylide pigments, feeding study, not carcinogenic)

- Copperphthalocyanine NTP decision on non-testing
  - CuPC: Haddow 1960: 8 weekly subcutaneous injections of 0.5 mg to 20 mice did not cause tumor formation in the 8-months observation period

Hazard data for members of all chemical classes (III) Reproductive toxicity, oral route

- Teratogenicity
  - Negative with PO 73
  - (negative with PR 57:1)
- Screening studies (OECD 421/422)
  - No adverse effects found for more than 15 pigments
- In-utero exposure/fertility study: no effects with Na-salt of PR 57:1
- Two-generation study
  - ECHA testing proposal for PO 73

Literature publications on toxicokinetic properties



Lack of dermal and oral absorption of Pigment Yellow 12

Decad GM, Snyder, CD, Mitoma C (1983). Fate of water-insoluble and water-soluble dichlorobenzidine-based pigments in Fischer 344 rats. Journal of Toxicology and Environmental Health 11: 455-465. Report date: 1983-01-01.

El Dareer, S. M.; Tillery, K. F.; Hill, D. L. (1984). Investigations on the disposition of oral doses of some waterinsoluble pigments. Bulletin of Environmental Contamination and Toxicology, 32 (2), 1984, 171-174

Mondino, A.; Achari, R.; Dubini, M.; Marchisio, M. A.; Silvestri, S.; Zanolo, G. (1978). Absence of dichlorobenzidine in the urine of rats, rabbits and monkeys treated with C.I. pigment yellow 13. Medicina del Lavoro, 69 (6), 1978, 693-697

Nony, C. R.; Bowman, M. C.; Cairns, T.; Lowry, L. K.; Tolos, W. P. (1980). Metabolism studies of an azo dye pigment in the hamster based on analysis of the urine for potentially carcinogenic aromatic amine metabolites. Journal of Analytical Toxicology, 4 (3), 1980, 132-140

Sagelsdorff, P.; Haenggi, R.; Heuberger, B.; Joppich-Kuhn, R.; Jung, R.; Weideli, H. J.; Joppich, M. (1996). Lack of bioavailability of dichlorobenzidine form diarylide azo pigments: molecular dosimetry for hemoglobin and DNA adducts. Carcinogenesis, 17 (3), 1996, 507-514

Bartsch, W.; Berger-Preiß, E.; Dasenbrock, C.; Ernst, H. (2001). Bioverfügbarkeit von Azopigmenten nach Aufnahme über die Atemwege. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Fb 929. Wirtschaftsverlag NW Bremerhaven

Hofmann, T.; Schmidt, D. (1993). Investigation of possible metabolism of pigment yellow 17, a 3,3'-dichlorobenzidine-based pigment, after inhalation exposure in rats. Archives of Toxicology, 67 (2), 1993, 141-144

Company data related to toxicokinetics

- Lack of accumulation of copper in kidney and liver upon subchronic feeding of a copper phthalocyanine pigment
- ^{14}C-Pigment Red 254 with MW of 357 g/mol is not significantly absorbed upon single oral dosing (intestinal passage within 24h)
- No internal organ discoloration observed
- No urine discoloration observed

No visual indication for absorption

- Poor solubility in water/fat is unfavourable for transport accross biological membranes

Summary

- Lack of systemic effects after ingestion observed in animal studies
- Systemic uptake upon skin contact not expected
- Relevant data for tattoo uses (intradermal application, decomposition products) not available

Thank you for your attention !