

2nd International Conference on Tattoo Safety

Tattoos and cancer: where are we in 2021?

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Conflicts of interests

- Expertises for Bayer, Beiersdorf and NOAS Bioderma
- Clinical studies for Laroche Posay and NOAS Bioderma
- I have tattoos

What we already know? (BfR 1)

Tattoo and cancer

Photoinstability of P.R. 22 and P.R. 9 after laser

- Irradiation of P.R. 22 and P.R.9 by a Nd:Yag laser
- Increase of byproducts
 - 2-methyl-5-nitroaniline
 - 2-5-dichloraniline
 - 4-nitro-toluene
 - 1,4-dichlorobenzene

Table 1 Amounts (μ g mL⁻¹) of decomposition products before and after laser irradiation of the pigments Cardinal Red (CR) or I8. The products found were 2,5-dichloroaniline (2,5-DCA), 1,4-dichlorobenzene (1,4-DCB), 2-methyl-5-nitroaniline (2-MNA), and 4-nitrotoluene (4-NT) [29]

		CR before irradiation	CR after irradiation	18 before irradiation	I8 after irradiation
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	µg/ml 2-MNA 4-NT 2,5-DCA 1,4-DCB	1.6±0.3 1.0±0.2 -	53.1±10.1 44.7±8.2	- - 11.8±0.3 < 0.5	- 79.6±1.4 32.6±0.4

• UVB and natural light on P.R. 22: detection of naphthol AS

Photoinstability of P.R. 22 and P.R. 9 after laser

- Photodecomposition of monoazo compounds (Pigment Red 22 and P.R. 9) induce the production of
 - 2-methyl-5-nitroaniline (2-MNA, hepatic dysfunction, mutagen for *salmonella*)
 - 4-nitro-toluene (4-NT, genotoxic on lymphocytes)
 - 2,5-dichloroaniline (2,5-DCA, nephrotoxic in the rat)
 - 1,4-dichlorobenzene (1,4-DCB, kidney cancer in the rat, liver cancer in the mouse)

Clinical relevance after laser removal in real life in human subjects?

Polycyclic aromatic hydrocarbons

- 19 commercial tattoo inks (HPLC, spectrometry)
 - Quantification of 20 PAH
 - 16 PAH detected
 - 7 PAH carcinogen B2 (USEPA carcinogenicity)

PAHs ¹	Mean value extracted [#g∕g]	Mean daily dietary intake (49) [/g/person]	Carcinogenidty USEPA (7)	Toxicity TEF (35)
Phenanthrene (12)	24.5 ± 6.0	1.54	D	0.001
Acenaphthylene (8)	14.5 ± 5.5	0.13	D	0.001
Benzo[b]fluoranthene (2)	4.5 ± 4.3	0.04	82	0.1
Pyrene (12)	4.4 ± 0.8	0.35	D	0.001
Anthracene (8)	3.3 ± 0.8	0.07	D	0.01
Fluoranthene (14)	2.8 ± 1.0	0.35	D	0.001
Chrysene (4)	1.7 ± 0.8	0.11	B2	0.01
Benz[a]anthracene (6)	1.6 ± 0.2	0.05	B2	0.1
Benzo[ghi]perylene (3)	1.2 ± 1.5	0.05	D	0.01
Indeno[1, 2, 3-cd]pyrene (2)	1.1 ± 1.0	0.03	B2	0.1
Acenaphthene (8)	0.9 ± 0.3	0.96	-2	0.001
Fluorene (6)	0.9 ± 0.2	0.59	D	0.001
Benzo[k]fluoranthene (2)	0.4 ± 0.2	0.01	B2	0.1
Benzo[a]pyrene (4)	0.3 ± 0.2	0.04	B2	1.0
Naphthalene (7)	0.3 ± 0.1	_2	c	0.001
Dibenzo[a,h]anthracene (1)	0.1 ± 0.1	0	82	1.0

Table 1. PAHs found in black tattoo inks

¹The number in brackets indicate the total number of inks in which the respective PAH was found.

²Data not available.

The bold characters highlight the probable or possible carcinogenic PAHs.

P.R. 22 in a tattooed mouse model

- In vivo study of UV decomposition and transportation of PR22
- 4 groups of mice
 - G1: Sacrificed at day 1
 - G2: Sacrificed at day 42
 - Solar radiation 32 days
 - G3a & G3b: Sacrificed at day 42
 - At D10, normal light exposure 32 days
 - G3a : Extraction of the pigments at D42
 - G3b : laser irradiation Nd:YAG 532 nm



Figure 2. Mice were tattooed with highly pure synthesized PR 22 (25% w/v) as shown by the four single pass tattoo 'stripes'(top). PR 22 has been transported to the lymph nodes causing a reddish coloration (bottom 2 panels).

• Day 1

• 36,5 µg PR22/punch

- Day 42 (group 3a)
 - 24,9 µg PR22/punch
 - Diminution of 32%
- Day 42 (group 2)
 - 9,9 µg/punch
 - Diminution of 60%
 - No carcinogens (2,5MNA, NT)
- Day 42 + laser
 - Detection of 2,5 MNA, 6-NT, NAS

Table 1. The values show the amount of PR 22 extracted 1 day after tattooing (group 1), 42 days after tattooing and exposure to solar radiation (group 2), or 42 days with room light followed without (group 3a) or with (group 3b) laser light irradiation. The respective standard deviation of the values (SD) is included in the table

Groups (conditions)	Amount per punch ¹ (mean) [µg]	Amount per animal (mean) [µg]	Standard deviation (SD) [%]	Loss of pigment [%]
Group 1 (1 day after	36.5	584.0	26	
Group 2 (42 days after tattooing	9.9	158.4	64	Corr. to group 3a 60 $P = 0.002^2$
Group 3a (42 days after tattooing, ambient light colu	24.9	398.4	24	Corr. to group 1 32 $P = 0.04^2$
Group 3b (42 days after tattooing + laser)	12.3	196.8	16	Corr. to group $3a$ 51 $P = 0.002^2$
5 mice - + Group 1 7 mice	So	olar light bient light	Group	stripes Genu
0 1	10 Time (days)	1	42	Laser Group

- « Natural » diminution of pigment concentration: 32%
 - Elimination through the epidermis (during the healing phase)
 - Transport in the rest of the body
 - Lymph node: yes
 - Further in the body: ?
 - Cutaneous *in situ* decomposition (UV, enzyme degradation)?
- Diminution after laser: 51%
 - only 8% of PR22 is found as 2,5-MNA and 4-NT
 - Other not extracted/analyzed products ?
- Diminution after UV: 60%
 - No decomposition product
 - In situ metabolism?
 - Spreading in the body ?
 - Other photochemical mechanism ?

Table 2. The values of the amount of the laser-induced decomposition products NAS, 2,5-MNA and 4-NT that were detected

Decomposition product	Amount per punch ¹ (mean) [#g]	Amount per animal (mean) [µg]	Standard deviation (%)
NAS	0.1	1.6	28
2,5-MNA	0.3	4.8	27
4-NT	0.1	1.6	28

¹Weight per punch: 35 mg.

The respective standard deviation (SD) of the values is indicated in this table.

Tattoo pigments migrate to draining lymph nodes a phenomenon known since before 1887

COMMUNICATIONS.

Etude microscopique et expérimentale sur les tatouages européens ;

PAR MM. G. VARIOT ET H. MORAU.

et qui sont placés entre les faisceaux du derme. Il semble que les particules colorantes sont fixées assez intimement sur la paroi externe des vaisseaux sanguins, car lors même que ces vaisseaux sont isolés dans les coupes, par écrasement, les parcelles ne s'en séparent pas. Nos préparations ne nous ont fourni aucun renseignement sur les rapports de ces particules avec les réseaux ou espaces lymphatiques du derme. Nous n'avons pas eu non plus l'occasion de voir l'état des ganglions lymphatiques correspondants. Mais les travaux antérieurs de Follin et de Virchow ont amplement démontré qu'un certain nombre de fragments colorés étaient charriés par les vaisseaux lymphatiques jusqu'aux ganglions.

Tattoo pigments migrate to draining lymph nodes





Nanoparticles in tattoos inks

CLINICAL AND LABORATORY INVESTIGATIONS

BJD British Journal of Dermatology

Tattoo inks in general usage contain nanoparticles

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Tattoos Today

From Eyelids to Ankles and Some in '3-D'

OTHER MEDICAL COMPLICATIONS

The subject of noninfectious complications has been reviewed.³ Because of the increasing incidence of melanomas and the possible relationship between trauma and the onset of localization of skin cancers, the dermatologist may expect to see more basal cell carcinomas and malignant melanomas occurring in tattoos.⁹⁻¹⁴

Norman Goldstein

THE LANCET Oncology



Epidemiology



K Saarinen (Lahti), O Saksela (Helsinki)

Fortuitous association between skin cancers and tattoos

What has happened since BfR 1?

Tattoo and cancer

Laser Irradiation of Organic Tattoo Pigments Releases Carcinogens with 3,3'-Dichlorobenzidine Inducing DNA Strand Breaks in Human Skin Cells

Journal of Investigative Dermatology (2018) 138, 2687–2690; doi:10.1016/j.jid.2018.05.031





	P.Y.138					P.O.13			
[pmol]	control	ruby (694 nm)	Nd:YAG (532 nm)	Nd:YAG (1064 nm)	control	ruby (694 nm)	Nd:YAG (532 nm)	Nd:YAG (1064 nm)	
HCN	<loq< th=""><th>4400 ± 2200</th><th>9200 ± 6600</th><th>2600 ± 1600</th><th><loq< th=""><th>1100 ± 200 ¶</th><th>16000 ± 7000</th><th>930 ± 1800</th></loq<></th></loq<>	4400 ± 2200	9200 ± 6600	2600 ± 1600	<loq< th=""><th>1100 ± 200 ¶</th><th>16000 ± 7000</th><th>930 ± 1800</th></loq<>	1100 ± 200 ¶	16000 ± 7000	930 ± 1800	
benzene	<loq< th=""><th>17 ± 7</th><th>23 ± 3</th><th>18 ± 3</th><th><loq< th=""><th>370 ± 40</th><th>1000 ± 900</th><th>150 ± 40</th></loq<></th></loq<>	17 ± 7	23 ± 3	18 ± 3	<loq< th=""><th>370 ± 40</th><th>1000 ± 900</th><th>150 ± 40</th></loq<>	370 ± 40	1000 ± 900	150 ± 40	
1,2,3,4- tetrachlorobenzene	<loq< td=""><td>13 ± 8</td><td>97 ± 50</td><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<></td></loq<></td></loq<>	13 ± 8	97 ± 50	<loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<></td></loq<>	<loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<>	<loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<>	<loq< td=""><td><loq< td=""></loq<></td></loq<>	<loq< td=""></loq<>	
pentachlorobenzene	<loq< td=""><td><loq< td=""><td>73 ± 31</td><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<></td></loq<></td></loq<></td></loq<>	<loq< td=""><td>73 ± 31</td><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<></td></loq<></td></loq<>	73 ± 31	<loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<></td></loq<>	<loq< td=""><td><loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<></td></loq<>	<loq< td=""><td><loq< td=""><td><loq< td=""></loq<></td></loq<></td></loq<>	<loq< td=""><td><loq< td=""></loq<></td></loq<>	<loq< td=""></loq<>	
xylene	130 ± 20	170 ± 70	180 ± 60	140 ± 50	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""></loq<></th></loq<>	<loq< th=""></loq<>	
НСВ	10 ± 3	10 ± 4	17 ± 5	9 ± 3	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""></loq<></th></loq<>	<loq< th=""></loq<>	
benzonitrile	1.3 ± 0.8	5.6 ± 1.7	4.3 ± 3.1	1.4 ± 1.0	7.3 ± 3.8	170 ± 60	610 ± 200	11 ± 11	
DCBD	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>220 ± 100</th><th>820 ± 340</th><th>3.2 ± 3.3</th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>220 ± 100</th><th>820 ± 340</th><th>3.2 ± 3.3</th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>220 ± 100</th><th>820 ± 340</th><th>3.2 ± 3.3</th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>220 ± 100</th><th>820 ± 340</th><th>3.2 ± 3.3</th></loq<></th></loq<>	<loq< th=""><th>220 ± 100</th><th>820 ± 340</th><th>3.2 ± 3.3</th></loq<>	220 ± 100	820 ± 340	3.2 ± 3.3	
aniline	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>130 ± 40</th><th>550 ± 230</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>130 ± 40</th><th>550 ± 230</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>130 ± 40</th><th>550 ± 230</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>130 ± 40</th><th>550 ± 230</th><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th>130 ± 40</th><th>550 ± 230</th><th><loq< th=""></loq<></th></loq<>	130 ± 40	550 ± 230	<loq< th=""></loq<>	
phenyl isocyanate	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>39 ± 57</th><th>680 ± 190</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>39 ± 57</th><th>680 ± 190</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>39 ± 57</th><th>680 ± 190</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>39 ± 57</th><th>680 ± 190</th><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th>39 ± 57</th><th>680 ± 190</th><th><loq< th=""></loq<></th></loq<>	39 ± 57	680 ± 190	<loq< th=""></loq<>	
2-chloroaniline	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>32 ± 5</th><th>99 ± 62</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>32 ± 5</th><th>99 ± 62</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>32 ± 5</th><th>99 ± 62</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>32 ± 5</th><th>99 ± 62</th><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th>32 ± 5</th><th>99 ± 62</th><th><loq< th=""></loq<></th></loq<>	32 ± 5	99 ± 62	<loq< th=""></loq<>	
2-aminobenzonitrile	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>6.2 ± 5.3</th><th>31 ± 12</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>6.2 ± 5.3</th><th>31 ± 12</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>6.2 ± 5.3</th><th>31 ± 12</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>6.2 ± 5.3</th><th>31 ± 12</th><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th>6.2 ± 5.3</th><th>31 ± 12</th><th><loq< th=""></loq<></th></loq<>	6.2 ± 5.3	31 ± 12	<loq< th=""></loq<>	
biphenyl	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>20 ± 8</th><th>83 ± 19</th><th>1.0 ± 1.0</th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>20 ± 8</th><th>83 ± 19</th><th>1.0 ± 1.0</th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>20 ± 8</th><th>83 ± 19</th><th>1.0 ± 1.0</th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>20 ± 8</th><th>83 ± 19</th><th>1.0 ± 1.0</th></loq<></th></loq<>	<loq< th=""><th>20 ± 8</th><th>83 ± 19</th><th>1.0 ± 1.0</th></loq<>	20 ± 8	83 ± 19	1.0 ± 1.0	
chlorobenzene	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>15 ± 6</th><th>64 ± 21</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>15 ± 6</th><th>64 ± 21</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>15 ± 6</th><th>64 ± 21</th><th><loq< th=""></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>15 ± 6</th><th>64 ± 21</th><th><loq< th=""></loq<></th></loq<></th></loq<>	<loq< th=""><th>15 ± 6</th><th>64 ± 21</th><th><loq< th=""></loq<></th></loq<>	15 ± 6	64 ± 21	<loq< th=""></loq<>	
3,3'-dichlorobiphenyl	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>24 ± 10</th><th>78 ± 19</th><th>1.5 ± 2.1</th></loq<></th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th><loq< th=""><th>24 ± 10</th><th>78 ± 19</th><th>1.5 ± 2.1</th></loq<></th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th><loq< th=""><th>24 ± 10</th><th>78 ± 19</th><th>1.5 ± 2.1</th></loq<></th></loq<></th></loq<>	<loq< th=""><th><loq< th=""><th>24 ± 10</th><th>78 ± 19</th><th>1.5 ± 2.1</th></loq<></th></loq<>	<loq< th=""><th>24 ± 10</th><th>78 ± 19</th><th>1.5 ± 2.1</th></loq<>	24 ± 10	78 ± 19	1.5 ± 2.1	

Archives of Toxicology https://doi.org/10.1007/s00204-020-02790-7

ANALYTICAL TOXICOLOGY



Treatments of a phthalocyanine-based green ink for tattoo removal purposes: generation of toxic fragments and potentially harmful morphologies

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ties and viscosities. The laser irradiation causes fragmentations of the green pigment and variations of the morphology of the ink aggregates, in terms of both size reduction and re-aggregations. Both processes are solvent dependent and differences can be reconducted to the initial sample, whether it is dried or extracted ink. The fragment compounds generated upon laser irradiation are toxic according to the Classification Labelling and Packaging regulations issued by the REACH-ECHA. The hazard statements include skin harm, irritation or allergy, which may be toxic or fatal if inhaled, cause eye damage, and irritation. One of the fragments, the 2,4,5,6-tetrachloro-1,3-benzonitrile, is suspected carcinogenic. Additional hexene derivatives fragments can



Pigment Green 7

Mouse models

Black ink with benzo(a)pyrene (BaP)

No. of

25

25

1

2

mice (n)

Table 1. Treatment schedule and results. Median number of days to onset of the first, second and third tumour in 50% of the mice in the groups. Interquartile range (Q1 = 25th percentile and Q3 = 75th percentile)

Median days to

50% of the mice

in a group $(Q_3 - Q_1)$

1st tumour in

No tumours

No tumours

Median days to

2nd tumour in

No tumours

No tumours

183 (170–183)

232 (219-240)

< 0.001*

50% of the mice

in a group $(Q_3 - Q_1)$

Median days to

50% of the mice

in a group $(Q_3 - Q_1)$

3rd tumour in

No tumours

No tumours

191 (183-196)

247 (224-+)

< 0.001*

hotocarcinogenesis	3	25	No ink	163 (148–183)	
	4	24	Black ink	212 (204–224)	
			100	<0.001*	
Group 3 compared w	vith (Group 4.			

Treatment

No ink

no UV

Black ink

no UV

*Group 3 compared with Group 4.

Group no.

Chemical

carcinogenesis

†Mice were sacrificed before this value could be obtained because of \geq 4 mm tumours outside the tattooed area.

Skin tumors are arising **later** on tattooed mice !







Skin tumors are arising **outside** the tattoos!

Fig. 4. (a) Mouse tattooed after 6 months of UVR three times per week. Squamous cell carcinomas are developing outside the tattood area. (b) Control mouse after 6 months of UV radiation three times per week. Squamous cell carcinomas are developing on the back and concentreated in the field corresponding to tattooed field as illustrated in Fig. 4a.

Lerche C, Photdermatol Photoimmunol Photomed 2015

Mouse models



Red ink with 2-anisidine

TABLE 1 Treatment schedule and results. Number of days to onset of the first, second and third tumors in 50% of the mice in the groups (onset). Median number of days for a given tumor to grow from 1 to 4 mm in diameter (growth rate). Interquartile range (IQR; 25th percentile and 75th percentile)

		First tumor		Second tumor		Third tumor	
Group	Treatment	Onset	Growth rate	Onset	Growth rate	Onset	Growth rate
1 (n=25)	No ink	-	-	-	-	-	-
	No UV						
2 (n=25)	Red ink	-	-	-	-	-	-
	No UV						
3 (n=24)	No ink	186	53	203	49	224	38
	+UV	(161-203)	(38-69)	(178-217)	(36-67)	(203-231)	(29-53)
4 (n=25)	Red ink	182	40	196	31	214	30
	+UV	(169-196)	(31-53)	(182-206)	(20-46)	(189-222)	(25-33)
P-value*		ns	ns	ns	.006	.043	.036

*Statistical P-value; Group 3 compared with Group 4. Ns: Non-significant P-value.

Third tumor arises faster

Lerche C, Exp Dermatol 2017

Nanoparticles in lymph nodes

Synchrotron-based ν -XRF mapping and μ -FTIR microscopy enable to look into the fate and effects of tattoo pigments in human skin



Ines Schreiver ¹, Bernhard Hesse², Christian Seim^{3,4}, Hiram Castillo-Michel², Julie Villanova², Peter Laux¹, Nadine Dreiack¹, Randolf Penning⁵, Remi Tucoulou², Marine Cotte² & Andreas Luch¹

	Donor	Tissue	Location	Al	Cr	Fe	Ni	Cu	Cd	other#
	1	Skin	dorsal	0.92	0.74	64.7	0.59	2.51	0.15	Ti
Autopsy from		LN	left axillary	1.97	0.43	125	0.28	2.98	0.35	Zn, Rb
donors	2	Skin	right leg	7.29	5.54	51.1	2.51	18.8	0.23	Ti
uonors,		LN	right inguinal	9.06	22.5	235	10.1	118	1.23	Ti, Mn
No data	3	Skin	right arm	3.39	2.73	84.7	1.61	67.5	0.17	Ti, I
about them!		LN	right axillary	5.08	13.9	221	6.74	28.7	0.28	Ti , Mn, Zn, Rb, I
	4	Skin	left arm	15.4	4.07	120	0.45	199	0.52	Ti, Br
No clinical impact thus		LN	left axillary	4.16	0.67	138	0.30	15.3	146	Ti, Br, Ba, Mn, W, Rb, Hg
for	Control 1	Skin	proximal	0.75	0.16	35.6	0.08	1.44	0.12	Pb
Idí		LN	axillary	1.11	0.31	64.4	1.09	12.9	0.47	
	Control 2	Skin	proximal	0.76	0.60	37.6	0.15	1.41	0.25	
		LN	axillary	0.24	0.14	74.7	0.09	2.48	0.83	Zn, Rb

Tattoo pigments in Kupffer cells (Liver)



Fig. 1. Study design flow chart: light microscopy (LM) and transmission electron microscopy (TEM) of tattooed skin, lymph nodes, lungs, liver, spleen, and kidneys.

Significance: detoxification or complication risk? No liver condition reported to tattoo pigments in humans



Sepehri M, Dermatology 2017

Commentary

Tattoo inks and cancer

Milena Foerster^a,*, Ines Schreiver^b, Andreas Luch^b, Joachim Schüz^a

^a Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France ^b Chemical and Product Safety, German Federal Institute for Risk Assessment (BfR), Berlin, Germany

The first epidemiological studies are now underway. Three Swedish case-control studies, funded by the national authorities will look retrospectively at a potential relationship between tattoo exposure and NHL, malignant melanoma and squamous-cell carcinoma of the skin, respectively. The International Agency for Research on Cancer (IARC) is collaborating with the large ongoing national general population cohorts, Constances in France (www.constances.fr) and NaKo in Germany (www.nako.de), to investigate tattoo-related cancer risks. These, and

Mélanomes sur tatouage : deux observations et revue systématique de la littérature

Melanoma within tattoos: Two cases and a systematic literature review

F. Cherkaoui El Baraka^a, N. Kluger^{b,c}, I. Ollivier^d, R. Bourgoin^e, M. Grossin^e, C. Zeboulon^a, C. Phan^a, C. Sin^a, E. Mahé^{a,*}

 $\bullet 34\,$ cases since 1938 to 2019 $\,$

- $\bullet 13$ years after tattooing (mean)
- O multiple melanomas on the same tattoo





Tattoo-Associated Basal Cell Carcinoma: Coincident or Coincidence

Philip R. Cohen^{a, b} Christof P. Erickson^c Nathan S. Uebelhoer^a Antoanella Calame^c

^aSan Diego Family Dermatology, National City, CA, USA; ^bDepartment of Dermatology, Touro University California College of Osteopathic Medicine, Vallejo, CA, USA; ^cCompass Dermatopathology, San Diego, CA, USA

 $\bullet 14\,$ cases since 1976 to 2020

 $\bullet 15$ years after tattooing (median)

• **O** multiple BCC on the same tattoo



Cosmetic Tattooing and Early Onset Basal Cell Carcinoma: A Population-based Case–Control Study from New Hampshire

Dorothea Torti Barton,^a Michael S. Zens,^b Eleni L. Marmarelis,^c Diane Gilbert-Diamond,^{b,d} and Margaret R. Karagas^{b,d}

- Hypothesis « the association between the presence of a tattoo and early onset basal cell carcinoma (< 50 y) would be confined to the *anatomic site* of the BCC »
- 21% (156/922) of the patients with early onset of BCC had a tattoo vs 26% (213/823) of the controls (... so having a tattoo is protective !)
- Misleading article and, after a reply to the authors, the authors have found an association **between having a BCC of the head and neck and a tattoo in the area** !



Keratoacanthomas and Squamous Cell Carcinomas on Tattoos: A Review of 42 Cases

Nicolas Kluger^{a, b} Bernard Cribier^c

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Table 1. Characteristics of 42 cases of tattoo-associated KAs and SCCs

Male gender %	23 (59.0)
Male female sex ratio	1.4
Malenemale Sex Tatlo	1.4
Median age, years	52
Mean age (SD), years	50.2 (12.3)
Past history of skin cancer $(n = 25)$	
Yes*	3 (12.0)
No	22 (88.0)
Actinic keratoses	3 (12.0)
Delay at onset after tattooing, months	
Range	Immediately - 120**
Median	1
Multiple lesions of KA	17 (40.5)
Color (out of 43 tattoos)	
Red	32 (74.4)
Black	3 (7.0)
Multicolored	7 (16.3)
NA	1 (2.3)
Localization (out of 41 tattoos)	
Upper limbs	16 (40)
Lower limbs	21 (53.6)
Trunk	1 (2.4)
Face (lips)	2 (4.8)
Laser removal prior to onset	2 (4.8)
Old tattoo touched-up prior to onset	2 (4.8)



Eruptive keratoacanthoma on red tattoos: the only non-fortuitous lesion ?





P.R. 270



Kluger, et al. Ann Dermatol Venereol 2017 Colboc, et al. J Eur Acad Dermatol Venereol 2020

Skin cancers in cohorts of tattooed patients with complications

Serup, 2017 n=405	Kluger, 2017 (1992-2016) n=31	Kluger, 2019 n=52	Kluger, 2021 (2016-2021) n=45	Rogowska, 2021 n=50	Van der Bent, 2021 n=301
Denmark	Finland	France	Finland	Poland	Netherlands
0% (n=0)	10% (n=3)	2.5% (n=3)	1% (n=1)	0% (n=50)	0.6% (n=2)
0.6% (n=3) KeratoAc	Melanomas	KeratoAc	B-cell lymphoma	-	BCC

Serup, et al. Dermatology 2017 Kluger. Dermatology 2017 Kluger, et al. J Eur Acad Dermatol 2019 Kluger, under submission, J Eur Acad Dermatol 2021 Rogowska, et al. accepted, Dermatology 2021 Van der Bent, et al. J Cosmet Dermatol 2021

Other cutaneous cancers

- Dermatofibrosarcoma n = 4
- Leiomyosarcoma n = 2
- Cutaneous lymphoma n = 1+1

De Antoni, Adv Skin Wound Care. 2020 Lastrucci I, et al. Indian J Dermatol. 2018 Reddy KK, et al. 2011 Baker PA, et al. Sarcoma. 2005 West CC, et al. J Plast Reconstr Aesthet Surg. 2009 Sangueza OP, et al. Am J Dermatopathol. 1992 Kluger, et al. Ann Dermatol Venereol under submission



Epidemiology





Fortuitous association between skin cancers and tattoos, except for keratoacanthomas in a specific group of individuals (mid aged, red color, sun exposure...)

Kluger N, Lancet Oncol 2012 Kluger N, Ann Dermatol Venereol 2017

Tattoos and Hematologic Malignancies in British Columbia, Canada



Freda M. Warner¹, Maryam Darvishian¹, Terry Boyle², Angela R. Brooks-Wilson^{1,3}, Joseph M. Connors¹, Agnes S. Lai¹, Nhu D. Le¹, Kevin Song¹, Heather Sutherland¹, Ryan R. Woods¹, Parveen Bhatti¹, and John J. Spinelli^{1,4}

ABSTRACT

Background: Tattoos may cause a variety of adverse reactions in the body, including immune reactions and infections. However, it is unknown whether tattoos may increase the risk of lymphatic cancers such as non-Hodgkin lymphoma (NHL) and multiple myeloma.

Methods: Participants from two population-based casecontrol studies were included in logistic regression models to examine the association between tattoos and risk of NHL and multiple myeloma.

Results: A total of 1,518 participants from the NHL study (737 cases) and 742 participants from the multiple myeloma study (373

cases) were included in the analyses. No statistically significant associations were found between tattoos and risk of NHL or multiple myeloma after adjusting for age, sex, ethnicity, education, body mass index, and family history.

Conclusions: We did not identify any significant associations between tattoos and risk of multiple myeloma, NHL, or NHL subtypes in these studies.

Impact: Though biologically plausible, tattoos were not associated with increased risk of NHL or multiple myeloma in this study. Future studies with greater detail regarding tattoo exposure may provide further insights.

Conclusions, today on November 19th 2021

- The toxicological studies have provided a high amount of anxiogenous data, that are NOT backed up to date by any clinical data
- The risk of skin cancer is today fortuitous
- The risk of systemic toxicity is currently unknown and (IMHO) overstated by *in vitro* data

Questions: is there a risk...



Necessity of follow – up of large cohort of tattooed individuals (biopsies, cancer registries) and robust *in vivo* studies in the skin of tattooed individuals

Isn't it matter of perspective?





Carcinogen 2B =possibly carcinogenic to human



Tableau 1 Carcinogénicité des hydrocarbures polycycliques extraits de l'article de Regensburger et al. [2] selon les classifications de l'US Environnemental Protection Agency (US EPA) [3] et de l'IARC [4].

	US EPA	IAR
Benzo[b]fluoranthène	B2	2B
Chrysène	B2	2B
Benz[a]anthracène	B2	2B
Indéno[1,2,3-cd]pyrène	B2	2B
Benzo[k]fluoranthène	B2	2B
Benzo[a]pyrène	B2	1
Dibenzo[a,h]anthracène	B2	2A

Classification de l'IARC: 1: carcinogène pour l'homme; 2A: carcinogène probable pour l'homme; 2B: carcinogène possible pour l'homme.

Furan



Caffeic acid

Nickel, Cobalt...

Some approved treaments in medicine,...



http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf

Nombre de nouveaux cas de cancer attribuables au mode de vie et à l'environnement en France en 2015 parmi les adultes de 30 ans et plus



Centre international de Recherche sur le Cancer



Source: IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lvon: International Agency for Research on Cancer. All rights reserved.



Thank you

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