Dioxin profiles in two Spanish families in follow-up studies of accidental poisoning by consuming contaminated olive oil

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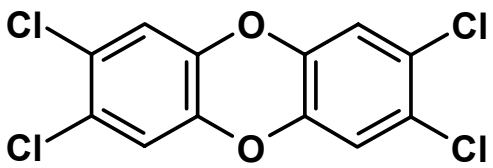
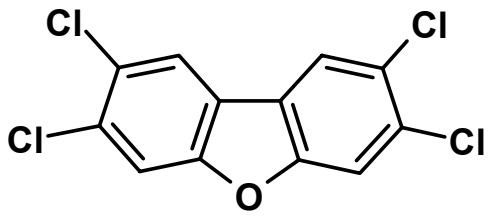
MRC Medical Research Council

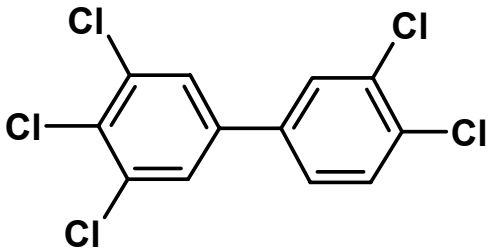
Environmental polyhalogenated dioxins, furans and dioxin-like PCBs

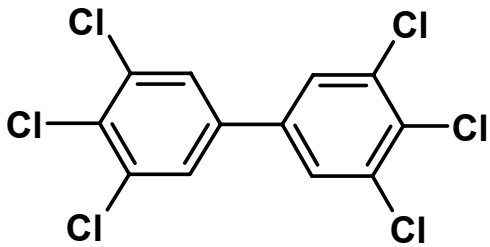


Dioxins (PDDs)



Furans (PDFs)





Biphenyls

- Human exposure episodes noted from 1940s
- First shown experimentally as toxic in the 1970s
- Now overwhelming amount of data

Dioxin exposure in humans

- **Chloracne-** most proven association
- **Hepatic toxicity-** increase in liver enzymes in plasma
- **Cardiovascular diseases-** in occupational exposure
- **Diabetes-** no consistent findings
- **Fertility and reproduction-**possible changes in sex ratio, endometriosis, sperm counts
- **Neurological/psychological**- possible but variable
- **Neurobehavioural**- possible
- **Immunological-** no consistent findings
- **Cancer-** regarded as probable human carcinogen but still political rather than perhaps scientific issue

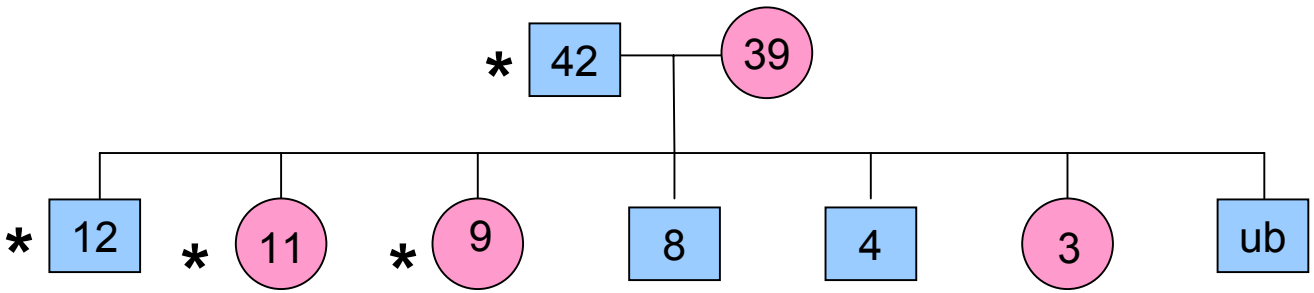
Chloracne in humans

- Chloracne occurs at acute high exposure; can take a long time disappear
- Characterised by pernicious, persistent cutaneous cysts and plugs
- Dose response not clear
- Some evidence for genetic susceptibility
- In AH-responsive mice, Hairless gene (*Hr*) is also required to see a response

Chloracne in Spanish family

- 1982 a whole family from Cordoba province appeared to have been poisoned by consuming cheap oil contaminated by storage in a plastic container used previously for other purposes.
- 1983 Sample of olive oil sent to MRC from Seville to confirm presence of HCB -which seemed odd.
- Pentachlorophenol and higher chlorinated dibenzo-*p*-dioxins also found.
- Eventually (1987), complete analysis of PDDs and PDFs in oil performed in Umea.

Chloracne in 1st Spanish family

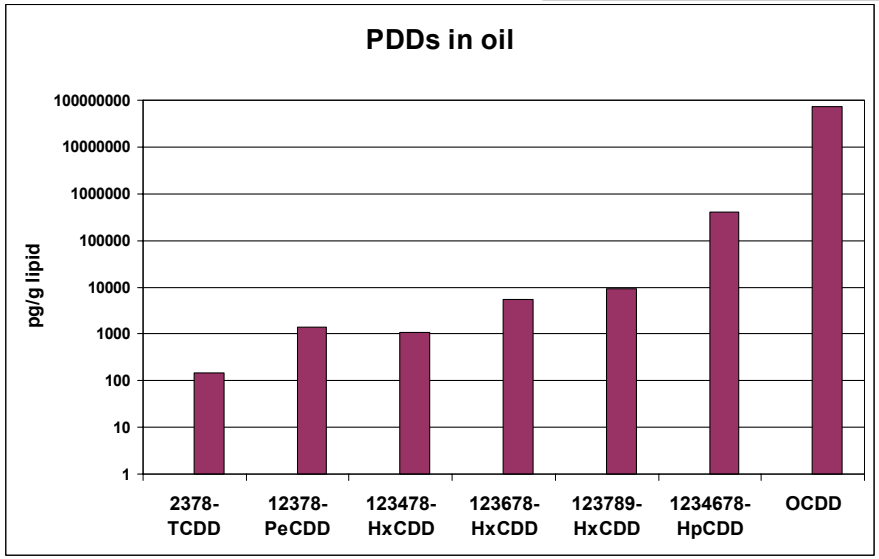


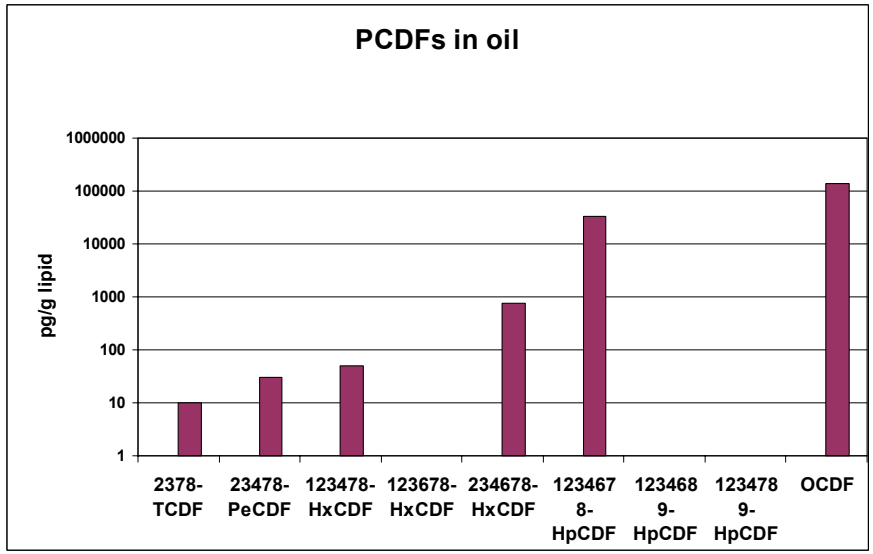
- Whole family presented to clinic in August 1982
- Eldest son was worst affected but all developed clear chloracne
- By November 1983 acneiform lesions mostly disappeared
- Boy born September 1982. Developed convulsions. Mother stopped feeding
- 1987 * Blood samples taken from worst original cases and combined to be analysed in Sweden

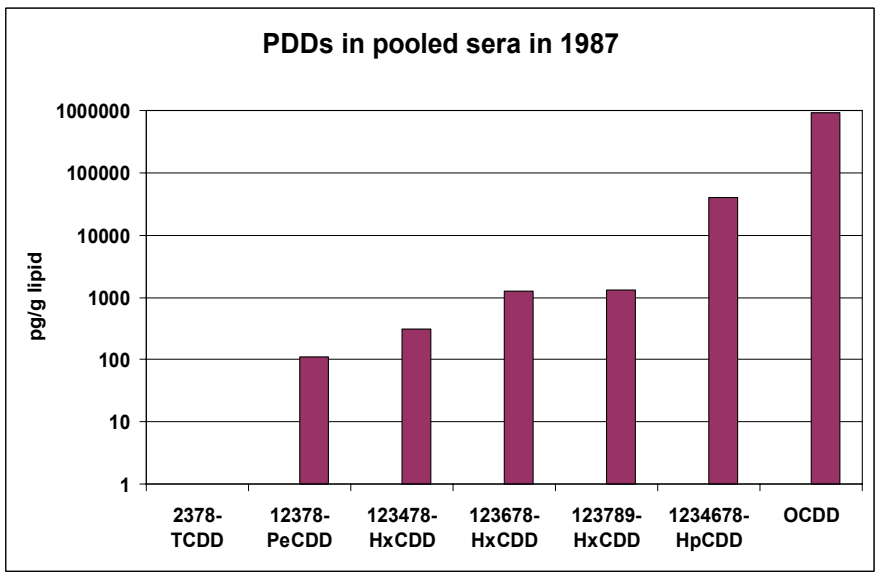
Rodriguez-Pichado et al 1991, Hum. Exp. Toxicol. 10, 311-322

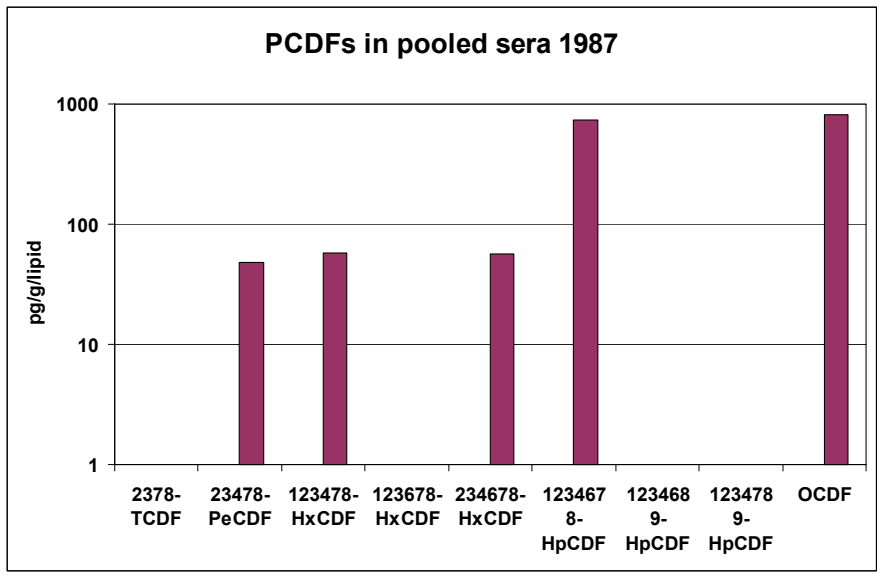
Chloracne in some of first family

First Spanish family









- Difficulty to assess true risks from PDDs when most clinical associations very weak
- Are there any biomarkers that can be detected in high body burden ‘dioxin’ cases that are not showing clinical symptoms?
- Marmosets very sensitive to changes in immune competence----humans?
- PDDs can affect hepatic haem synthesis –here?

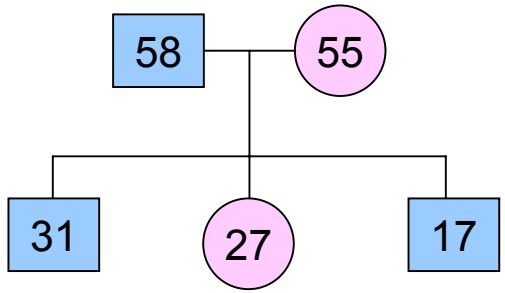
FRAMEWORK 1993-1997

Assessment of early signs of biological action following human exposure to polyhalogenated dibenzo-*p*-dioxins and related substances

Cohorts chosen all reported with chloracne and likely to have high body burdens of dioxins

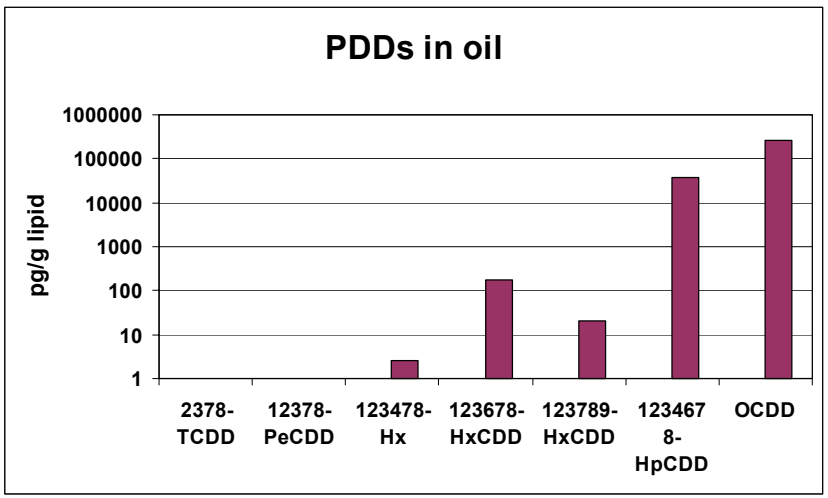
- Family from Seville, Spain, poisoned by contaminated olive oil.
- Trichlorophenol workers, Spolano, Czech Republic, exposed to TCDD.
- Cohort of workers engaged in PCBs manufacture, Slovak Republic.
- Small cohort, Chesterfield, UK, possibly exposed to TCAB and TCAOB in 3,4-dichloroaniline manufacture.(No dioxins were detected).
- Austrian workers exposed to TCDD in manufacture of 2,4,5-trichlorophenol. (Neuberger et al 1999, Environ. Res. A, 81, 206-214)

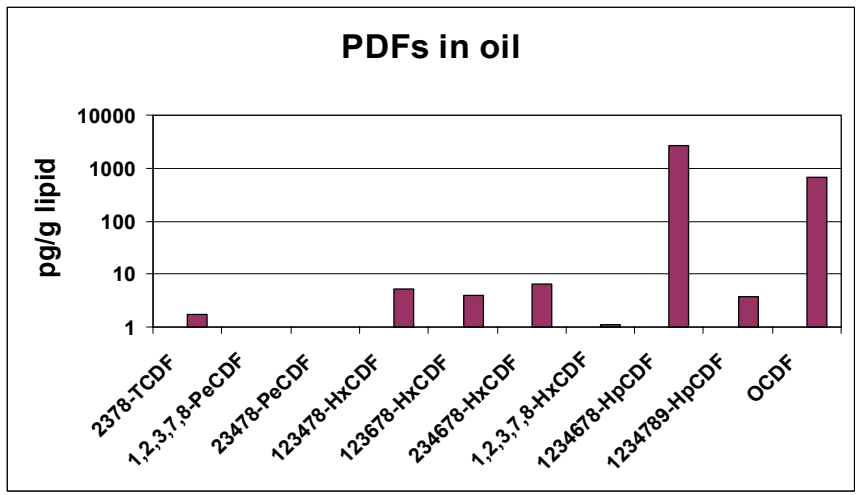
Second Spanish family



- 1990 2nd family referred to dermatological clinic apparently poisoned in a similar but unrelated incident

- Not as severe as family 1

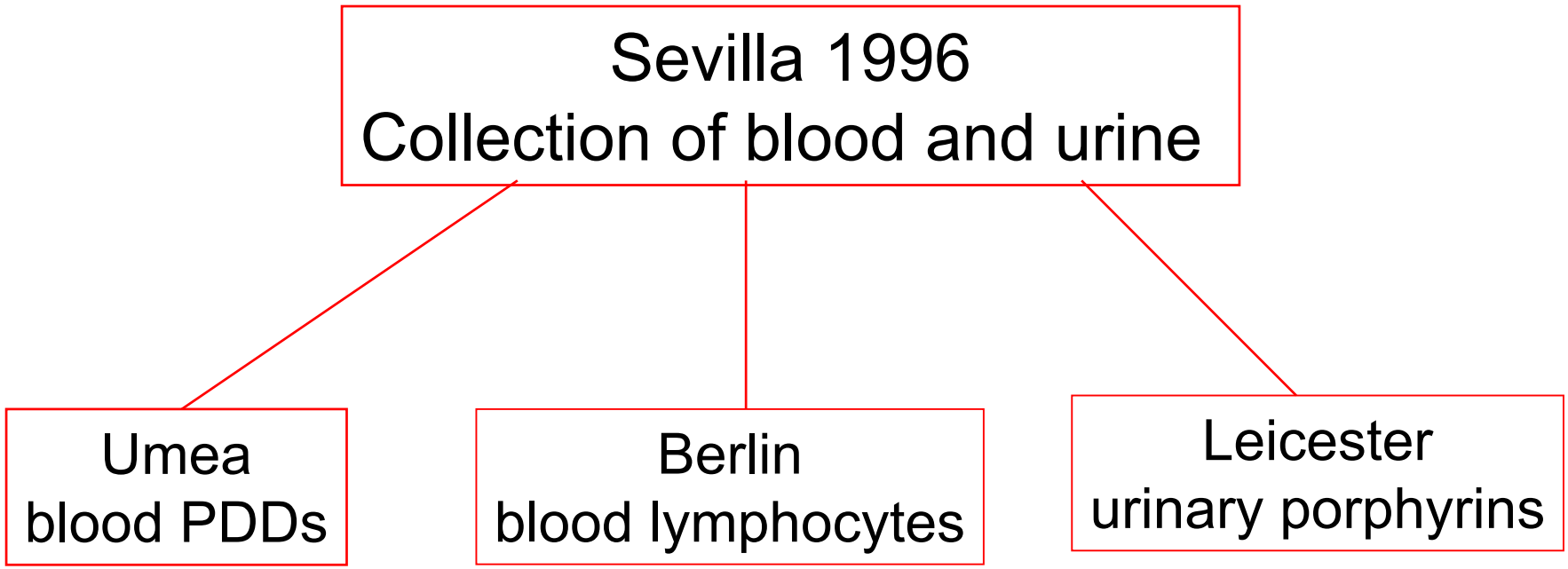




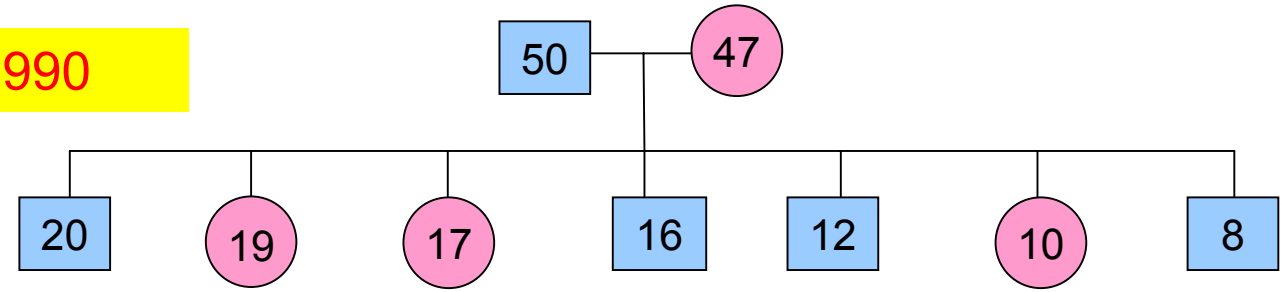
Aims with Spanish families

- Compare blood levels of PDDs and PDFs in 1990 with levels in 1996 to see how much and what had declined.
- Determine whether any immunological components or functions abnormal with high PDDs/PDFs body burden
- Early work had suggested presence of novel porphyrin in the Spanish urine that might indicate residual hepatic toxicity

Protocol


Sevilla 1996
Collection of blood and urine
Umea
blood PDDs
Berlin
blood lymphocytes
Leicester
urinary porphyrins

Family 1 1990



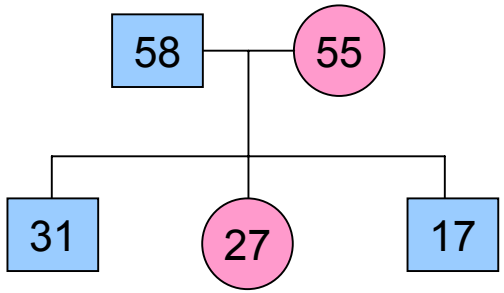
Age	50	47	20	19	17	16	12	10	8
Kg	100	80	54	54	56	51	43	35	22
pg/g lipid									
2378-TCDD	2.8	ND	ND	ND	ND	ND	ND	ND	ND
12378-PeCDD	77	28	71	25	24	22	ND	ND	ND
123478-HxCDD	220	77	240	78	71	52	30	32	29
123678-HxCDD	860	360	1100	370	350	370	180	180	50
123789-HxCDD	920	330	230	140	200	50	48	26	ND
1234678-HpCDD	46000	16000	14000	8200	9400	2100	2600	1800	1600
OCDD	300000	240000	210000	180000	140000	20000	28000	17000	14000

1996

* * *

Age	56	53	26	25	23	22	18	16	14	3	2
Kg	102	70	60	63	58	65	68	53	43		
pg/g/lipid											
2378-TCDD	2.4	<1.1	<1.5	<1.3	<1.2	<1.4	<1.6	<1.2	<1.8	<9.9	<8.0
12378-PeCDD	54	29	16	9.5	21	9.4	8.7	8.0	6.1	45	30
123478-HxCDD	150	76	53	32	59	12	18	16	<6.2	110	27
123678-HxCDD	640	400	240	150	310	150	130	100	45	350	140
123789-HxCDD	880	400	32	68	210	20	30	30	28	160	42
1234678-HpCDD	37000	14000	1400	3100	4600	190	390	420	220	2600	720
OCDD	660000	380000	37000	110000	130000	6100	13000	9000	3000	45000	11000

Family 2



(1990)

Age	58	55	31	27	17
Kg	74	75	67	58	83
pg/g lipid					
2378-TCDD	1.7	ND	ND	ND	ND
12378-PeCDD	32	12	13	28	11
123478-HxCDD	150	52	55	94	17
123678-HxCDD	3500	1700	1300	2700	1700
123789-HxCDD	1200	480	360	800	390
1234678-HpCDD	54000	62000	53000	84000	64000
OCDD	170000	190000	190000	280000	180000
2378-TCDF	2.6	4.9	1.7	3.6	3.1
23478-PeCDF	26	16	6.1	18	25
123478-HxCDF	44	27	18	36	23
123678-HxCDF	17	11	6.5	13	8.8
234678-HxCDF	50	37	20	13	22
1234678-HpCDF	2300	2400	2100	13	3000
1234789-HpCDF	27	26	13	13	21
OCDF	1200	1800	1200	13	1300

(1996)

Age	64	61	33	23
Kg	72	73	56	90
pg/g lipid				
2378-TCDD	<0.97	<1.1	<1.1	<0.27
12378-PeCDD	13	14	7.2	0.51
123478-Hx	61	49	22	2.5
123678-HxCDD	1500	1400	1000	180
123789-HxCDD	550	250	150	20
1234678-HpCDD	66000	26000	16000	38000
OCDD	440000	330000	180000	270,000
2378-TCDF	4.1	3.2	7.5	1.7
23478-PeCDF	21	14	25	<0.25
123478-HxCDF	21	14	10	5.1
123678-HxCDF	9.0	6.00	5.0	3.9
234678-HxCDF	8.8	5.6	5.1	6.7
1234678-HpCDF	1600	1000	840	2700
1234789-HpCDF	7.8	<3.2	<2.8	3.7
OCDF	NA	N/A	N/A	670

Immunological components and functions

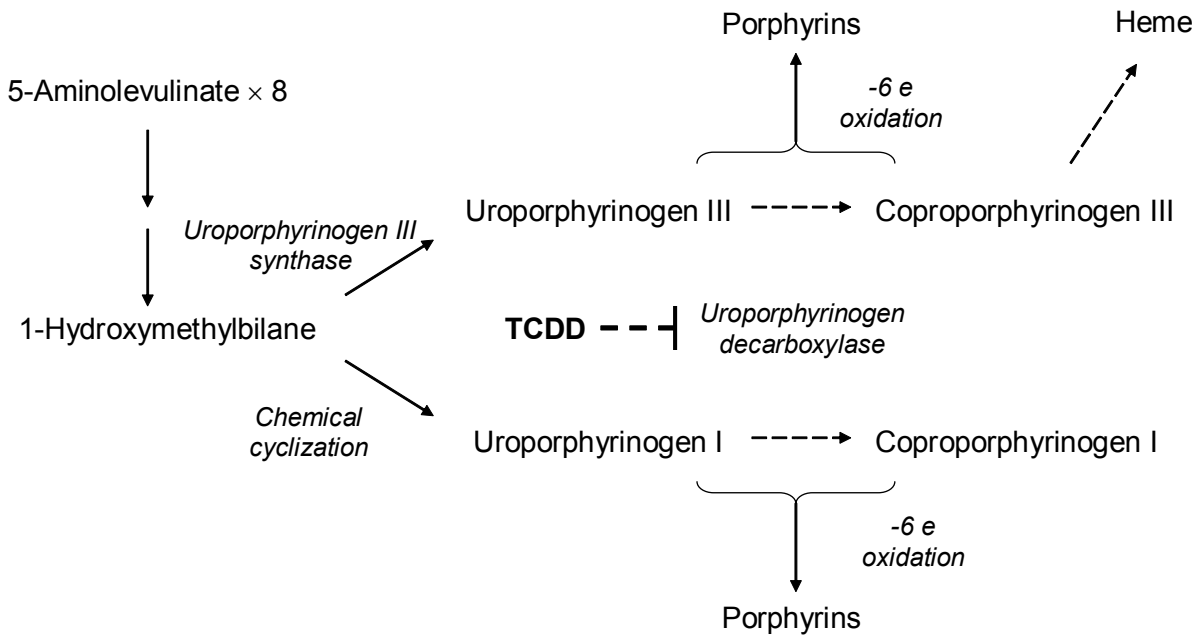
- Spanish volunteers categorised as:

4 Older (48-65) Ref. population of 39 selected from control Seveso data

9 Younger (18-32) Ref. population 44.

- 4/9 of younger group had higher number of lymphocytes cf Seveso, but sub-populations depleted. However,higher exposures in ref.range.
- No variations from standards and refs for older.

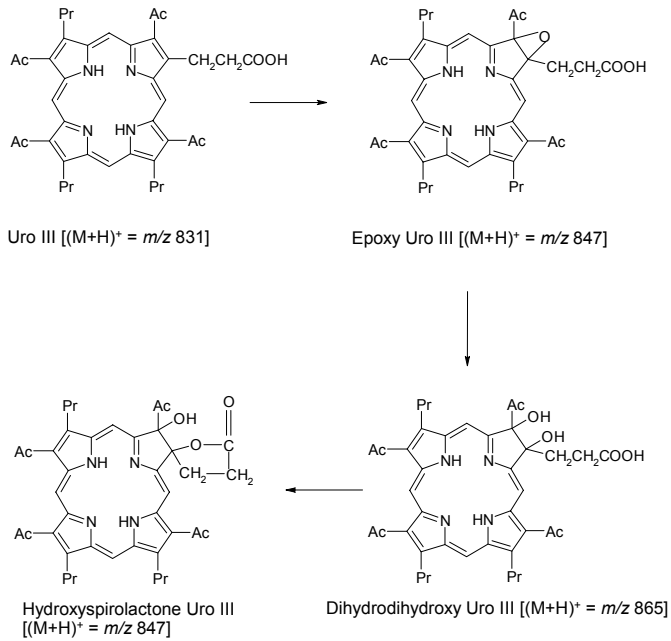
Urinary porphyrins



In preliminary studies, a porphyrin of unknown structure was observed in urine from 1st family.

1996

- 5 volunteers (all 1st family) showed abnormal porphyrin, probably an oxycoproporphyrin
- Similar was detected in urine from some Austrian patients
- Recent work has shown new oxyuroporphyrins in TCDD mouse liver



Summary

- 2 Spanish families showed continued retention of higher PDDs and to a less extent PDFs
- Decline in blood levels over 6 years was observed in some family members in others rises were observed
- No clear correlation of levels with immuno competence was observed.

Thanks

- EU
- C. Rappe, M. Hansson, A. Rodriguez-Pichado, A. Ferrer-Dufol, D. Neubert, R. Neubert, J.B. Greig, C.K. Lim