Universiteit Utrecht

Reprotoxic health effects among oncology nurses:

Tasks versus Dermal Exposures to Antineoplastics

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Background

- Parliamentary questions on reproductive health effects from occupational exposure to chemicals in 1995 led to an epidemiological study among hospital workers
- Study population consisted of oncology and operating theatre nurses employed in 1990-1997
- Questionnaire-based study among 5546 nurses from whom 4393 responded
- Focus was on the last pregnancy
- Exposure study was performed, but not used in epi-analysis

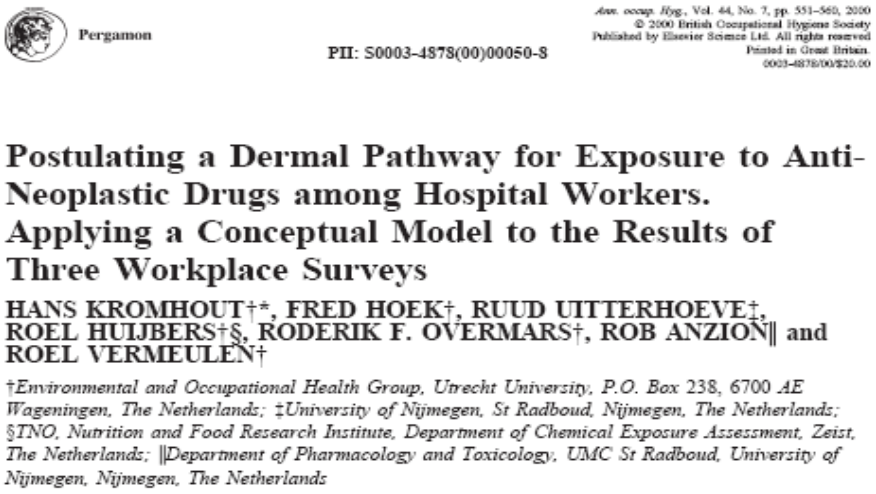
Background

- Main results for oncology nurses (249 pregnancies with 229 life births) in comparison with a reference group of nurses not exposed to antineoplastics:
  - No increased risk for prolonged time to pregnancy; OR=0.9 (0.5-1.5)
  - SA; OR=1.4 (0.8-2.5)
  - Early birth; OR=1.2 (0.6-2.2)
  - Low birth weight; OR=1.9 (0.8-4.1)
    - **Preparing OR=16.7 (3.4-81.6)** (3 out of 14)
    - **Cleaning OR=2.9 (1.2-7.2)** (13 out of 161)
  - Birth defects; 1.0 (0.4-2.4)
    - **Preparing OR=5.1 (1.1-23.6)** (2 out of 15)

Background

- Results of the study led to interventions and follow-up studies
  - Manual on safe handling of antineoplastic drugs (1997)
  - Study: Exposure to antineoplastic agents in the hospital, state of the art of control measures (2001)
  - Policy regulations for working with antineoplastic drugs (2001)
  - Covenants between Ministry of Social Affairs and Employment and Dutch Hospitals

New exposure studies focused mainly on dermal exposure



Pergamon

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Postulating a Dermal Pathway for Exposure to Anti-Neoplastic Drugs among Hospital Workers. Applying a Conceptual Model to the Results of Three Workplace Surveys

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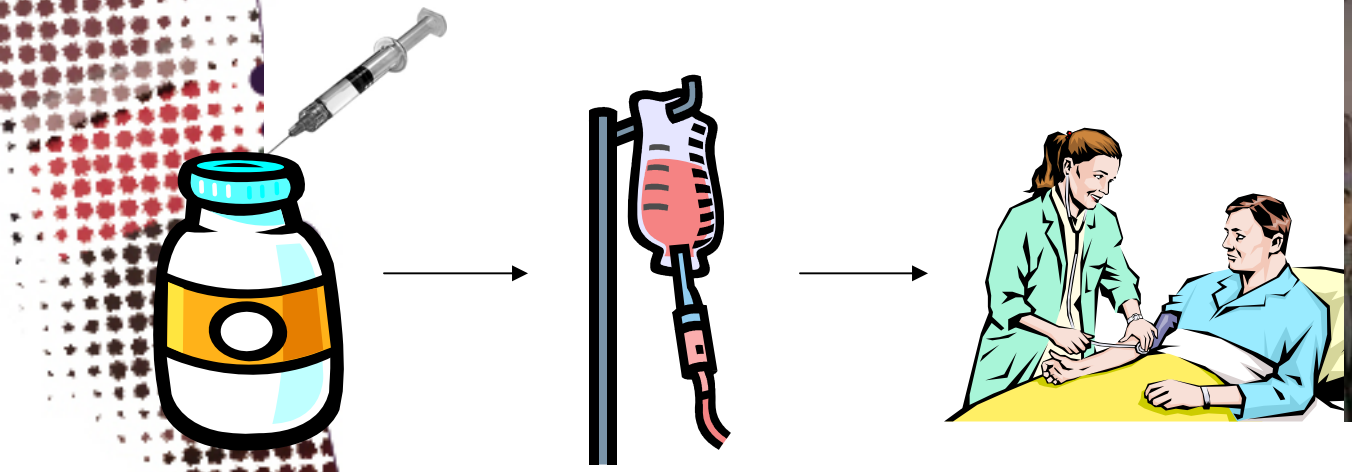
Background

- Nurses are exposed to antineoplastic drugs, mainly via the skin
- Epidemiological studies in the past focused on job title (oncology nurse)
- Recent dermal exposure studies enabled us to use a quantitative dermal exposure assessment approach
- Would it be possible to link this succesfully to reproductive outcome?

Route of the drugs



Preparation

Administering

Nursing

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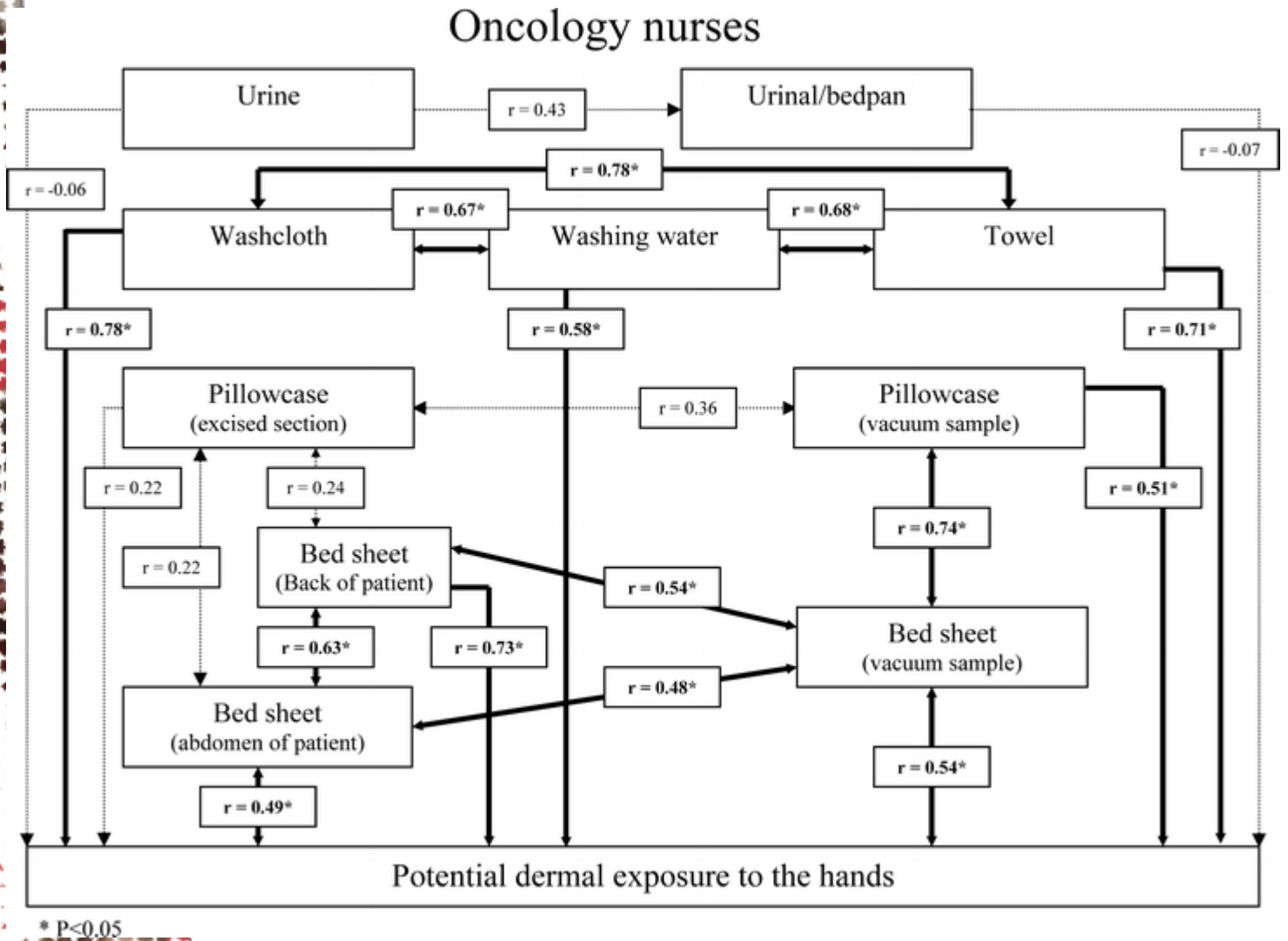
It can be a rather complicated picture



* P<0.05

Study participants

- Nurses of reproductive age (22-37 yr) were selected from hospital personnel records
- Employed at least 2 months between 1990 and 1997 as oncology nurse (exposed to antineoplastic drugs) or at one of the departments: orthopedics, gynecology, surgery (reference group)
- Background exposure for nurses not working with antineoplastic drugs, but working at a department where these drugs were frequently used

Original study design

- Reproduction toxic effects:
  Self-reported questionnaire on pregnancy outcomes

- Exposure assessment:
  Task-based dermal exposure measurement results multiplied by self-reported task frequency (from questionnaire)

Questionnaire

- Questionnaire focused on last pregnancy while working in a hospital. Questions on:
  - Pregnancies
  - Lifestyle factors
  - Working conditions
  - Specific questions on working with antineoplastic drugs

- Reproduction toxic effects studied:
  - Time to pregnancy
  - Spontaneous abortion (miscarriage < 20^{th} week)
  - Stillbirth (miscarriage $\geq 20^{th}$ week)
  - Premature delivery (life birth $< 37^{th}$ week)
  - Low birth weight ($\leq$2500 grams)
  - Gender offspring (%boys)
  - Congenital anomalies (according to EUROCAT)

Exposure assessment

- Glove pairs were collected and analyzed for cyclophosphamide (CP) during:
  - Preparation
  - Administering
  - Handling patients' urine

- Complemented by dermal exposure measurements (Fransman et al., 2005):
  - Washing patient
  - Removing bed sheets
  - Cleaning toilet

- Weekly exposure = Σ ($Exposure_{task}$ x $Glove\ protection_{task}$ x Task Frequency)

measurements **questionnaire**

Statistical analysis

- SAS statistical software
- Geometric mean dermal exposure per task
  (½*LOD for values<LOD)
- Survival analysis for time to pregnancy (PROC PHREG)
- Parameter estimates and crude and adjusted odds ratios for dichotomised pregnancy outcomes (PROC LOGISTIC)
- Further explored by using nonparametric regression modelling (smoothing; PROC GAM)

Results (study participants)

- Participation from 83 out of 121 Dutch hospitals (69%)
- 4,393 of the 5,546 selected female nurses of reproductive age completed and returned the questionnaire (79%)
- 2,426 nurses had been pregnant between 1990 and 1997 at least once (2,021), or were pregnant during survey (198), or had tried to get pregnant (207)
- 1,519 nurses met the requirements for one of the exposure categories, background exposure, or the non-exposed reference group
- No obvious differences between exposed and referent nurses in personal, lifestyle, and work related factors

Results (exposure assessment)

Task	1996-1997 (this survey) CP on gloves [µg] N	GM	Range	2001-2003 (Fransman et al., 2005) CP on gloves [µg] N	GM	Range	CP on skin of hands [µg] N	GM	Range
Preparation	8	27.0	1.79-207.4	26	0.07	0.01-5.42	26	0.01	0.01-0.04
Administering	29	0.04	0.01-26.3	0	-	-	0	-	-
Handling patient urine	11	0.09	0.01-8.45	26	0.02	0.01-0.13	26	0.02	0.01-0.14
Washing patient	0	-	-	10	0.19	0.04-0.75	10	0.03	0.01-0.10
Removing bed sheets	0	-	-	8	0.02	0.01-0.05	8	0.02	0.01-0.17
Cleaning patient toilet	0	-	-	19	0.06	0.01-0.80	19	0.01	-

Results (exposure assessment)

Task	1996-1997 (this survey) CP on gloves [μg] N	GM	Range	2001-2003 (Fransman et al., 2005) CP on gloves [μg] N	GM	Range	CP on skin of hands [μg] N	GM	Range	Exposure estimates No gloves used	Gloves used
Preparation	8	27.0	1.79-207.4	26	0.07	0.01-5.42	26	0.01	0.01-0.04	31.9	4.87
Administering	29	0.04	0.01-26.3	0	-	-	0	-	-	0.05	0.01
Handling patient urine	11	0.09	0.01-8.45	26	0.02	0.01-0.13	26	0.02	0.01-0.14	0.19	0.10
Washing patient	0	-	-	10	0.19	0.04-0.75	10	0.03	0.01-0.10	0.21	0.03
Removing bed sheets	0	-	-	8	0.02	0.01-0.05	8	0.02	0.01-0.17	0.05	0.02
Cleaning patient toilet	0	-	-	19	0.06	0.01-0.80	19	0.01	-	0.07	0.01

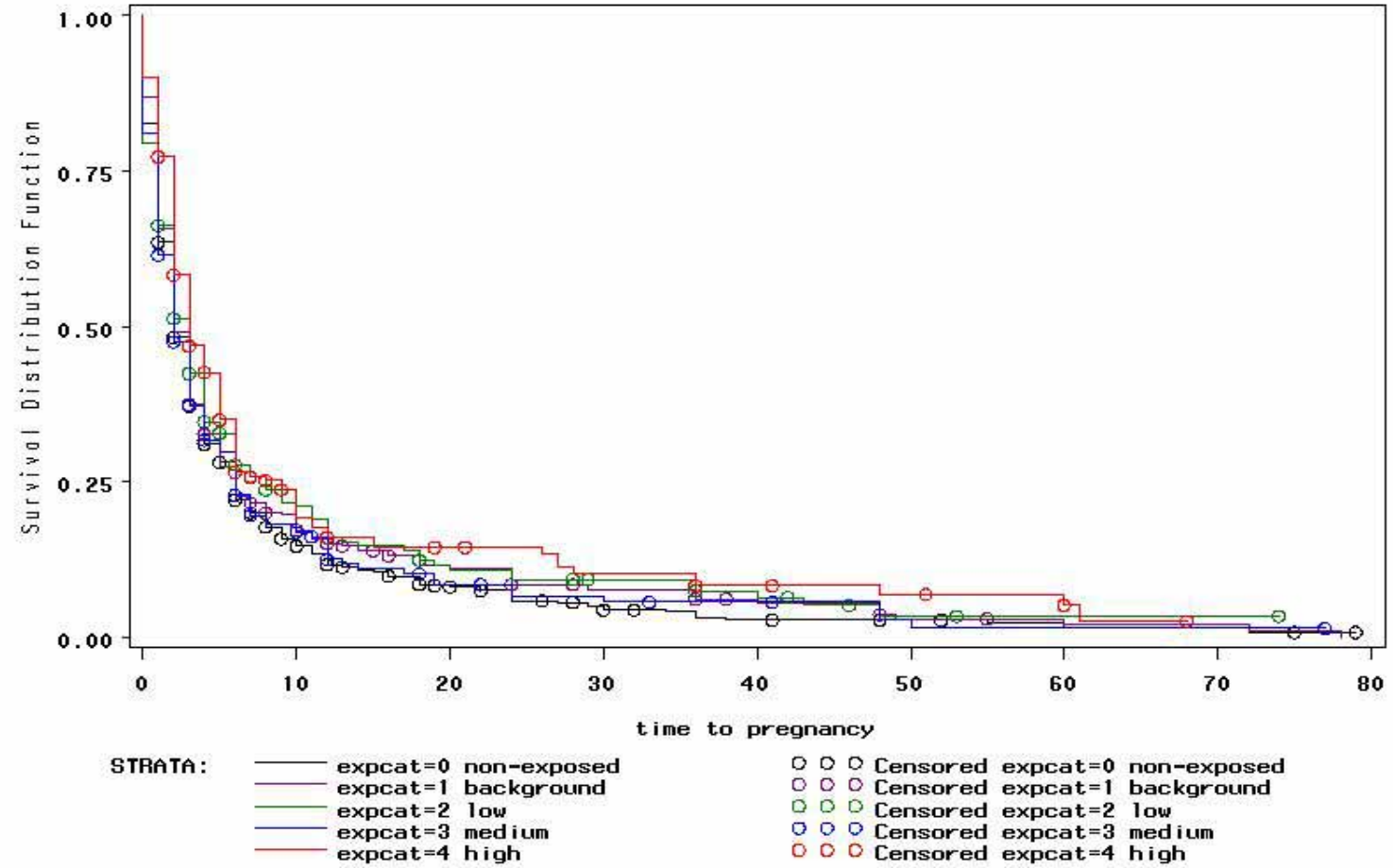
Exposure distribution

- Oncology nurses were divided into three exposure categories based on the exposure distribution:
  - High (>0.74 μg) N=177
  - Medium (0.20 μg<exp<0.74 μg) N=177
  - Low (≤0.20 μg) N=178
- Background exposure N=324
- Non-exposed reference group N=663

Results

	Non-exposed (N=663)		Background exposure (N=324)		Low-exposed (N=178)		Medium-exposed (N=177)		High-exposed (N=177)	
	Mean	**HR**	**Mean**	**adj-HR** (95% CI)	**Mean**	**adj-HR** (95% CI)	**Mean**	**adj-HR** (95% CI)	**Mean**	**adj-HR** (95% CI)
Time to pregnancy (months)	5.5	1.0	6.5	0.9 (0.8-1.1)	6.6	0.9 (0.8-1.1)	5.5	1.0(0.8-1.2)	7.2	**0.8 (0.7-0.97)**
	%	**OR**	**%**	**adj-OR** (95% CI)	**%**	**adj-OR** (95% CI)	**%**	**adj-OR** (95% CI)	**%**	**adj-OR** (95% CI)
Spontaneous abortion (<20 wk)	5.5	1.0	6.5	1.0 (0.6-1.9)	6.8	1.3 (0.6-2.7)	5.6	1.1 (0.5-2.4)	6.9	1.2 (0.5-2.5)
Still birth (≥20 wk)	0.4	1.0	0.4	0.9 (0.1-10.1)	1.4	3.3 (0.5-24.6)	1.4	4.2 (0.6-31.1)	0.7	1.9 (0.2-21.3)
Premature delivery (<37 weeks)	6.3	1.0	3.6	0.6 (0.3-1.2)	6.8	1.1 (0.5-2.4)	6.9	1.1 (0.5-2.4)	8.8	1.4 (0.7-2.9
Low birth weight (≤2500 gr)	4.0	1.0	3.3	0.9 (0.4-2.0)	7.0	1.8 (0.8-4.2)	4.0	1.0 (0.4-2.7)	8.1	2.0 (0.9-4.5)
Gender offspring (% boys)	50.6	1.0	53.1	1.1 (0.8-1.5)	55.1	1.2 (0.8-1.8)	48.4	0.9 (0.6-1.4)	53.6	1.1 (0.7-1.7)
Congenital anomalies	3.2	1.0	0.4	**0.1 (0.02-0.97)**	3.9	1.2 (0.4-3.4)	3.1	1.0 (0.3-3.0)	5.3	1.7 (0.7-4.6)

Time to pregnancy



Results (linear relations)

	All subjects (N=1519)	
	$\beta_{\ln(exp)}$	P-value
Time to pregnancy	**-0.02***	**0.036**
Spontaneous abortion	0.01	0.772
Stillbirth	0.18	0.078
Premature delivery	**0.08***	**0.042**
Low birth weight	**0.10***	**0.027**
Gender offspring	0.005	0.827
Congenital anomalies	0.11	0.056

*** P<0.05**

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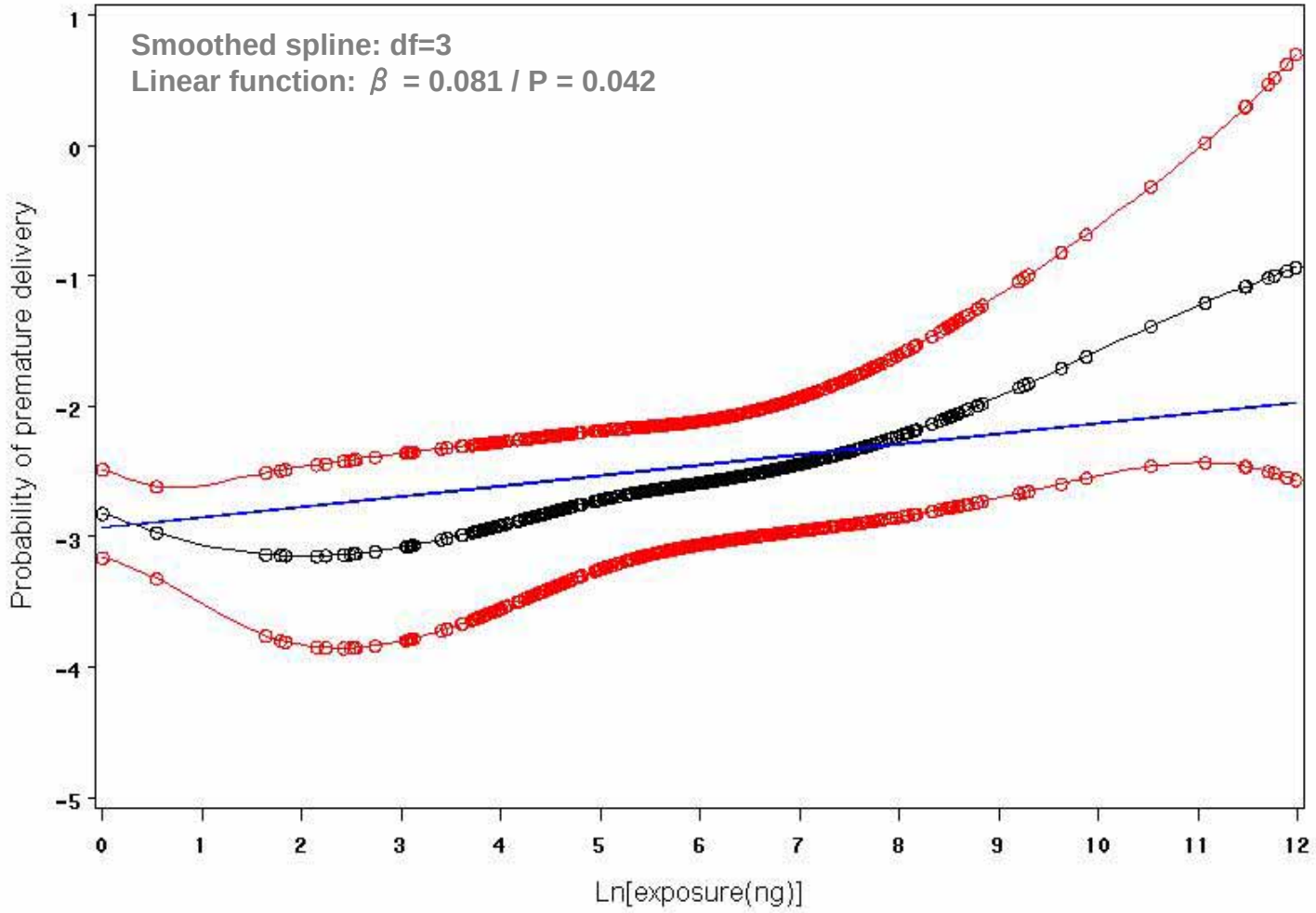
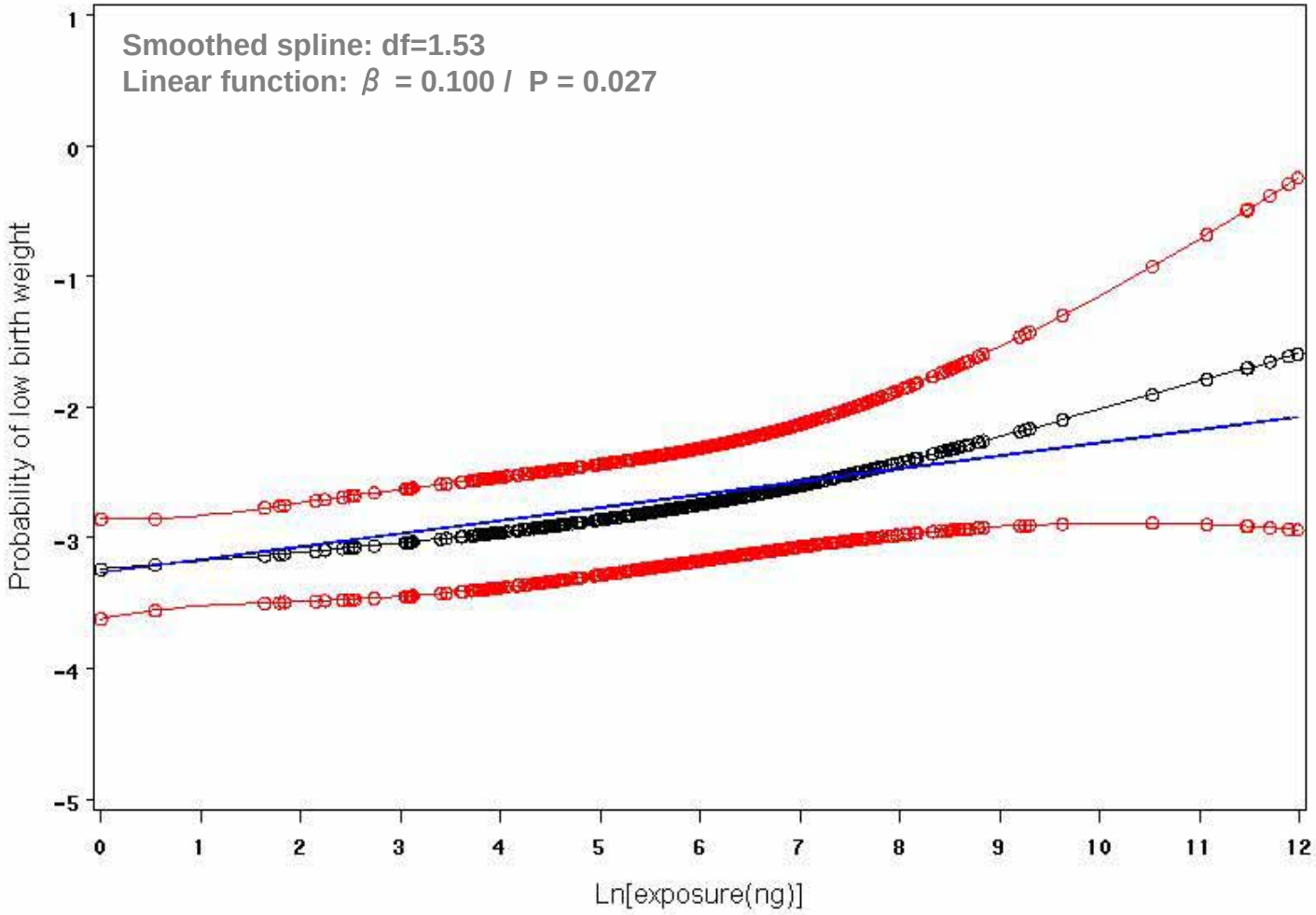
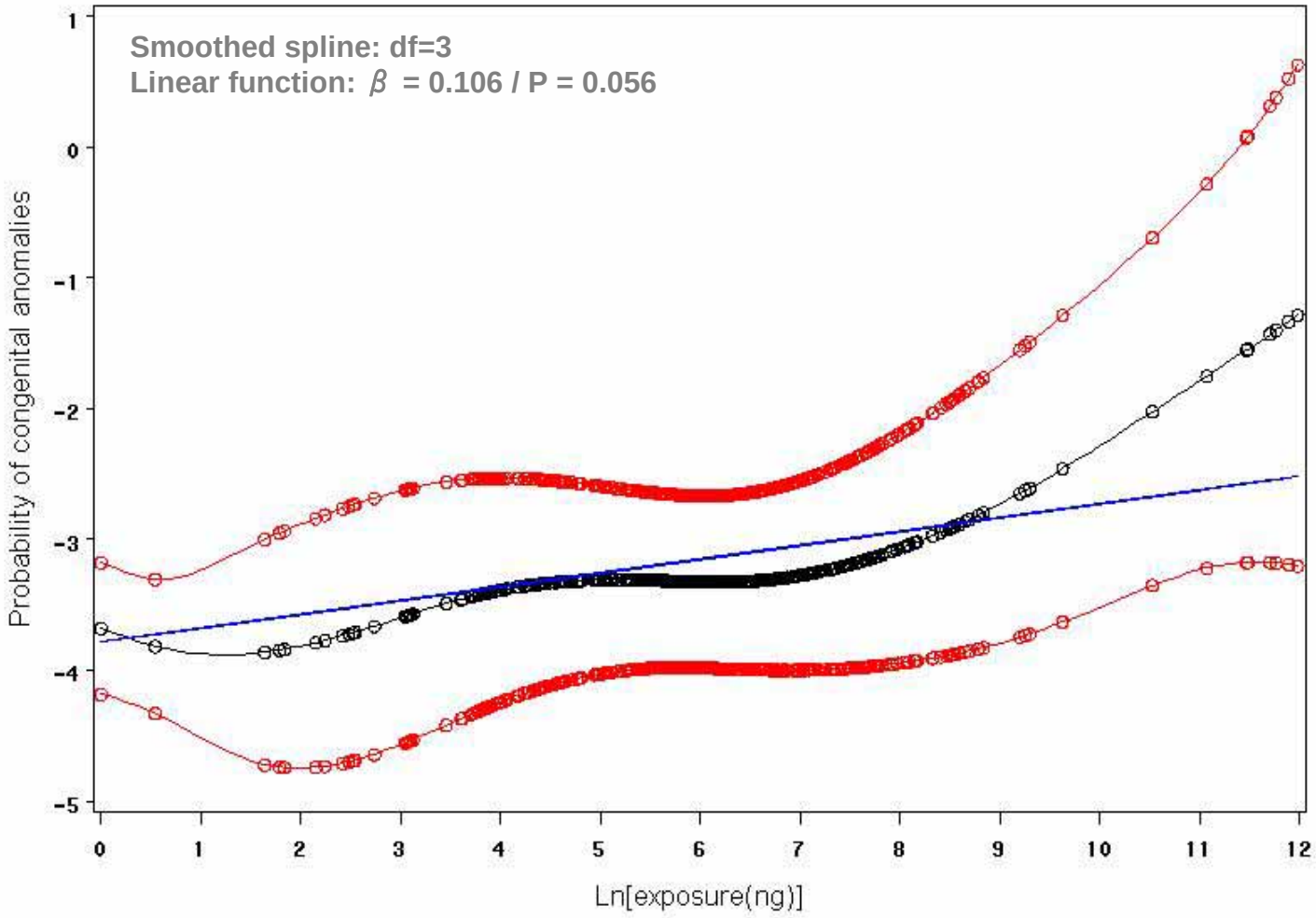
Smoothing plot (premature delivery)



Smoothing plot (low birth weight)



Smoothing plot (congenital anomalies)



Conclusions

- Two-months prolonged time to pregnancy among nurses with high dermal exposure to antineoplastic drugs (>0.74 µg/week) compared with non-exposed nurses
- Positive linear relations between dermal exposure to antineoplastic drugs and risk of premature delivery, low birth weight, and congenital anomalies
- Penalized smoothed spline plots confirm these results and suggest even higher risks at extreme exposures
- Spontaneous abortion, still birth, and gender offspring seemed not related to exposure to antineoplastic drugs

Conclusions

- This is the first study to show quantitative relations between exposure to antineoplastic drugs among oncology nurses and reproductive health effects
- This study showed the possibility of combining task-based exposure measurements and task frequency for exposure assessment purposes and to investigate dermal exposure-response relations
- Current dermal exposure levels are still high and should be lowered by preventing exposure during nursing tasks involving treated patients

And it is not over yet

Maternal occupational exposures and risk of spontaneous abortion in veterinary practice

A Shirangi,[1] L Fritschi,[2] C D J Holman[1]

- Of 762 veterinary clinics 73 (9.6%) used antineoplastic drugs
- 39 clinics (5.1%) only prescribed the drugs while 34 (4.5%) administered drugs in the clinics
- Safety measures were far from adequate
- Using antineoplastic drugs for pets is heavily being promoted

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