

# Risk of thyroid cancer following $^{131}\text{I}$ exposure in childhood – *Belarus/Russia/EU/IARC case-control study*



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# List of collaborators

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# Number of cases and controls interviewed by region

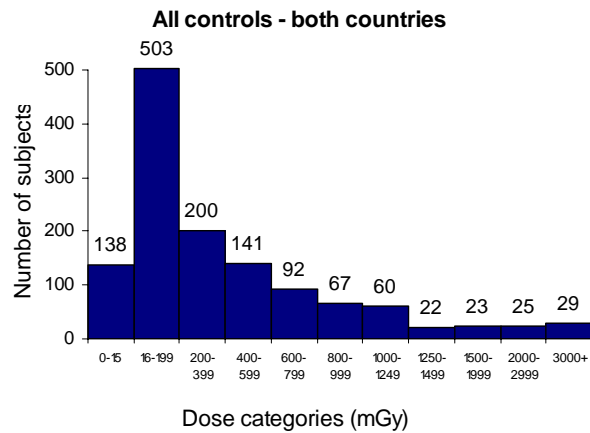
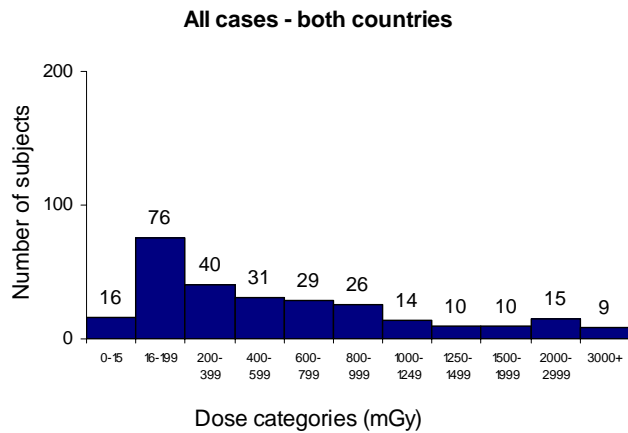
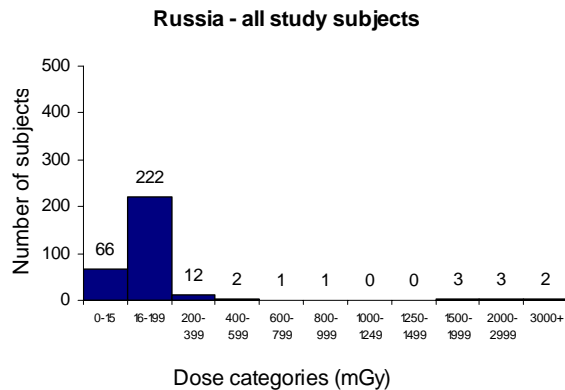
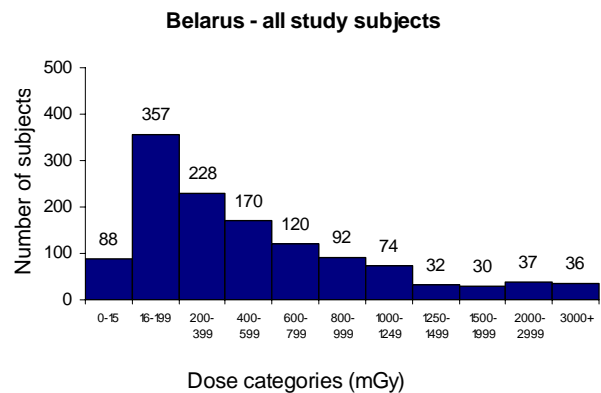
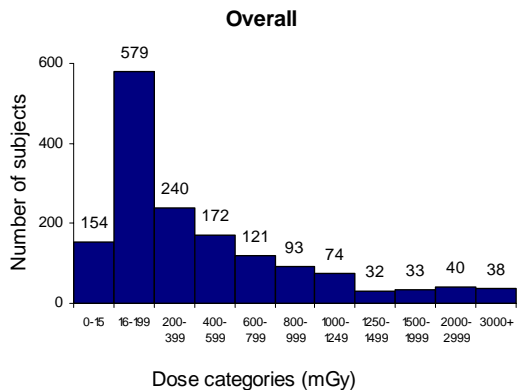
| Status                       | Belarus |         | Russian Federation |        |      |      | Total |
|------------------------------|---------|---------|--------------------|--------|------|------|-------|
|                              | Gomel   | Mogilev | Bryansk            | Kaluga | Orel | Tula |       |
| No. of cases                 | 188     | 32      | 11                 | 10     | 18   | 17   | 276   |
| No. of controls              | 877     | 167     | 49                 | 39     | 87   | 81   | 1300  |
| Age at exposure (cases only) |         |         |                    |        |      |      |       |
| <2 y                         | 69      | 10      | 4                  | 1      | 1    | 2    | 87    |
| 2-4 y                        | 59      | 8       | 3                  | 2      | 3    | 5    | 80    |
| 5-9 y                        | 45      | 3       | 2                  | 4      | 6    | 6    | 66    |
| 10-14 y                      | 15      | 11      | 2                  | 3      | 8    | 4    | 43    |
| Sex (cases only)             |         |         |                    |        |      |      |       |
| Boys                         | 74      | 7       | 6                  | 4      | 6    | 5    | 102   |
| Girls                        | 114     | 25      | 5                  | 6      | 12   | 12   | 174   |

*Note: results presented here are for subjects aged < 15 ATA – in Russia  
about 30 additional cases were also interviewed who were 15-18 ATA*



center  
in epi  
epi

# Total thyroid dose among study subjects (mGy)





# Thyroid dose distribution (mGy)

|             |         | Median | Maximum |
|-------------|---------|--------|---------|
| I-131       | Belarus | 355.7  | 9 528   |
|             | Russia  | 39.4   | 5 257   |
| Short-lived | Belarus | 1.6    | 534     |
|             | Russia  | 0.1    | 26      |
| External    | Belarus | 2.4    | 98      |
|             | Russia  | 0.9    | 31      |
| Long-lived  | Belarus | 1.2    | 42      |
|             | Russia  | 0.4    | 12      |
| Total       | Belarus | 365.4  | 10 163  |
|             | Russia  | 40.4   | 5 314   |



# Analyses

## ● Main analyses

- Conditional logistic regression
- Adjustment for confounders
  - ✓ By stratification
- Effect modification
  - ✓ Modelled as interaction
  - ✓ Likelihood ratio test to evaluate significance
- Reference dates for controls: date of diagnosis of matched case

*... all time-dependent variables calculated up to reference date*



# Analyses (cont'd)

## ● Main analyses

➤ Log-linear risk model:  $OR = \exp [\beta * f(d)]$

... also ERR model:  $OR = 1 + \beta * f(d)$

➤ Main dose-response analyses

✓ Continuous exposure measures

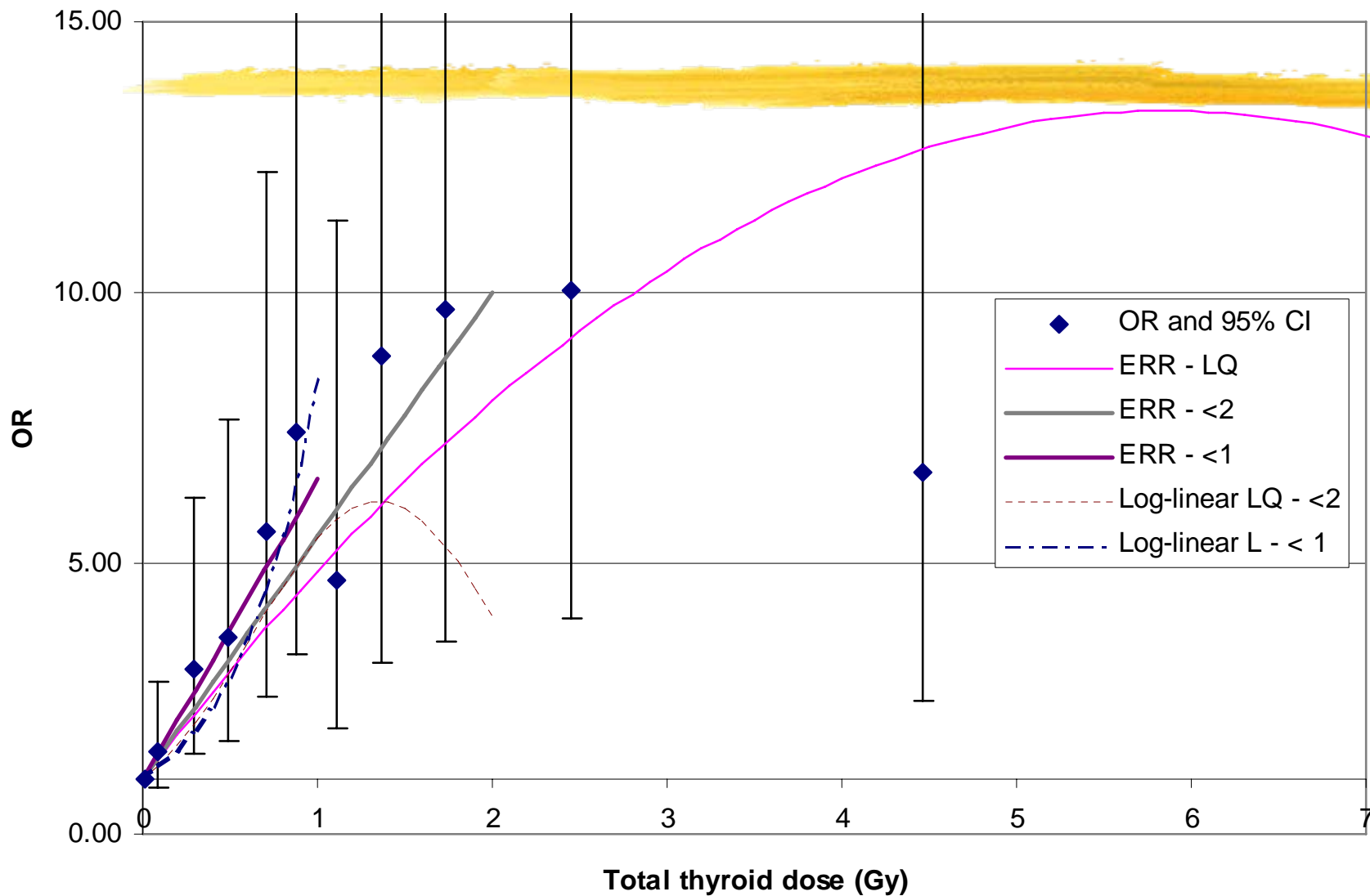
- Departures from linearity explored with polynomials

✓ Lag of doses – 5 years (long lived isotopes, external)

✓ Risk estimates – MLE ; Confidence intervals: likelihood-based ; p-values: 2-sided



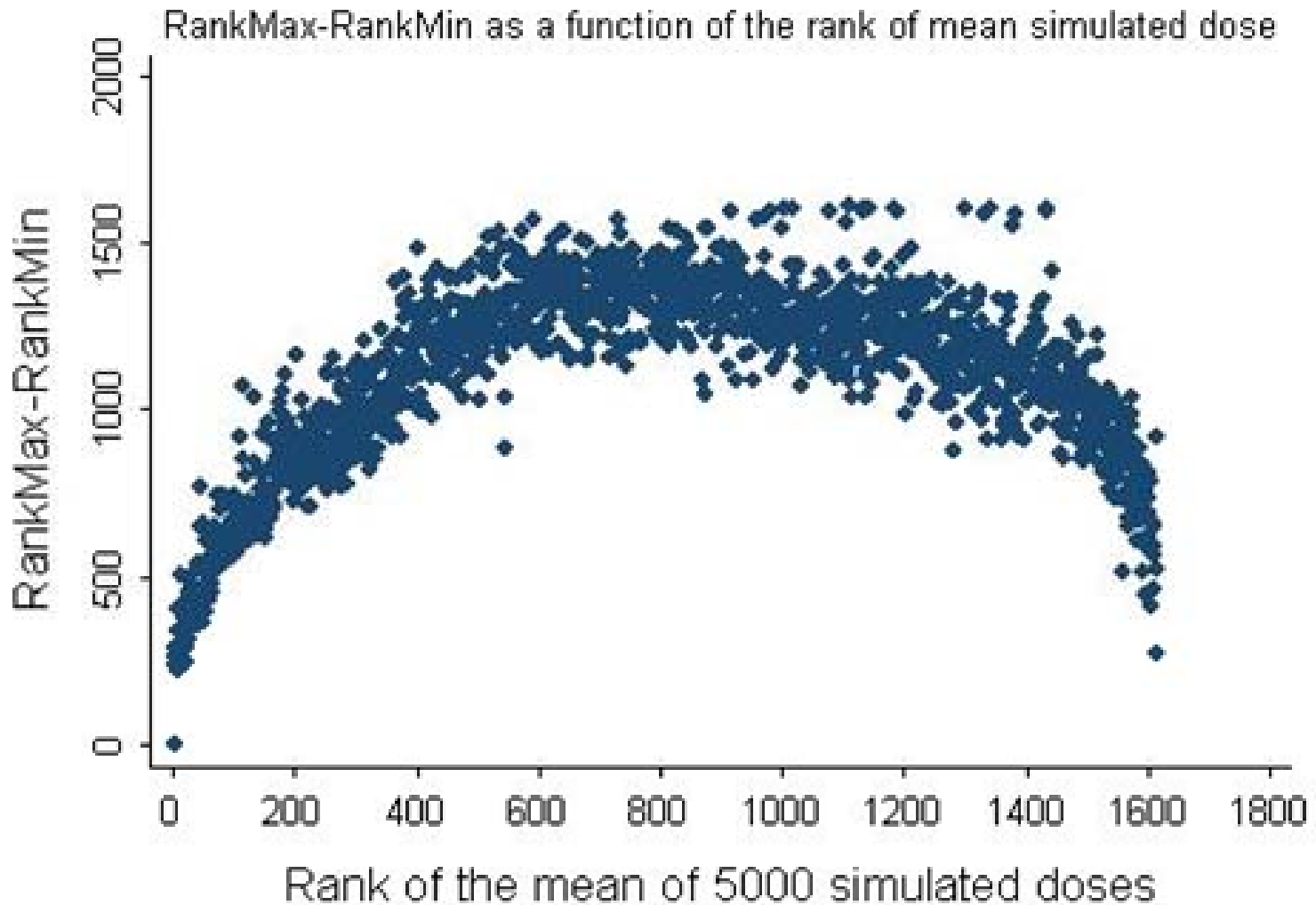
# Summary of dose-response relationship





# Approach for taking into account uncertainties

- Initial proposal – MCML method we have used before (*Stayner et al 2008*)
  - X thousand realisations of the doses taking into account (in a 2 stage fashion) the shared and unshared errors





# Approach for taking into account uncertainties

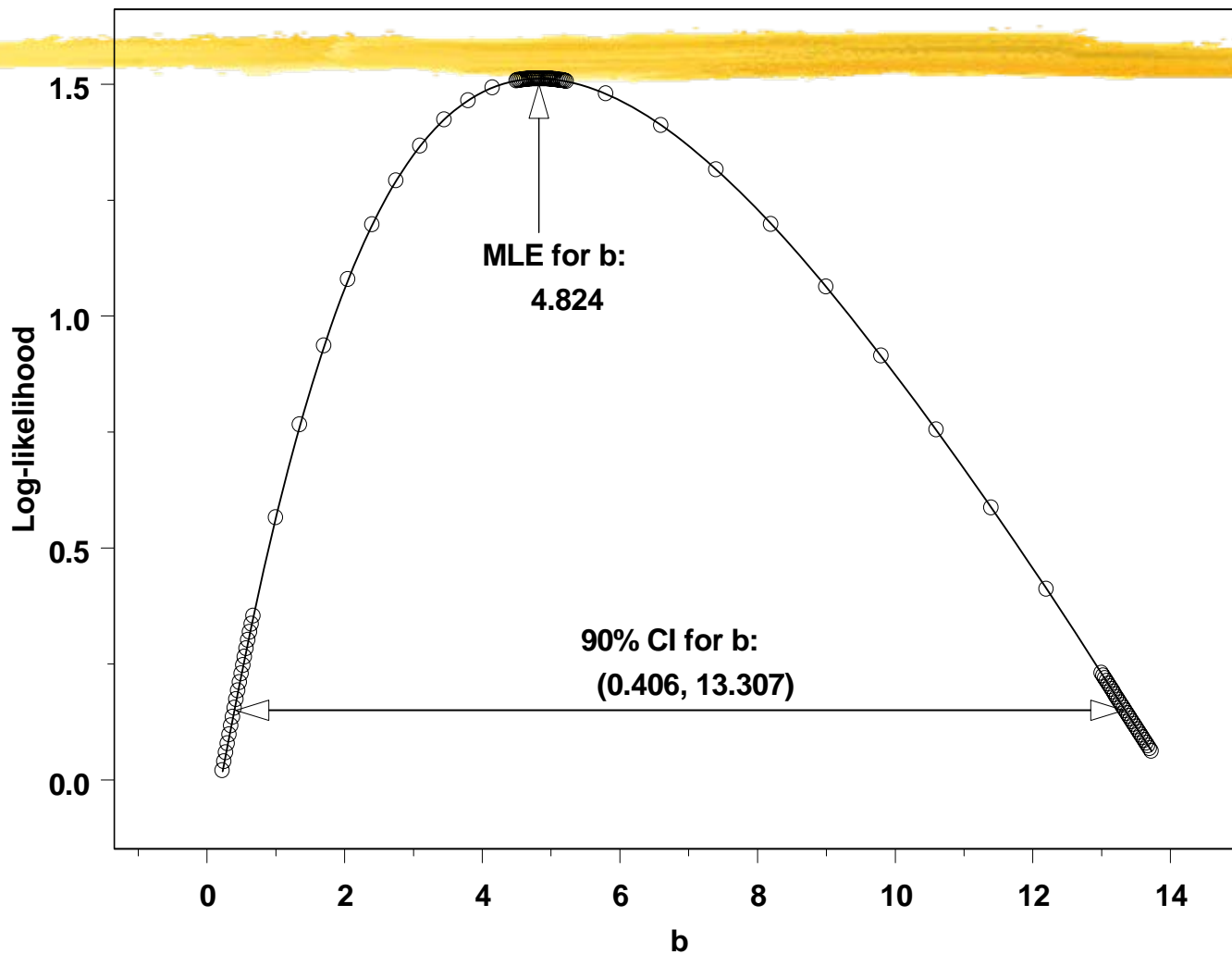
## ● Initial proposal – cont'd

⇒ X thousand data sets –

- ✓ Derive the profile likelihood for each
- ✓ Average the profile likelihoods over all the realisations
- ✓ Obtain the MLE and 95% CI



**Figure 3: Profile likelihood, MLE and 90% CI for b from the 10,000 simulations**





# Problems

## ● Dose-response is not linear ...

- Depending on scale, the best fitting polynomial is either L-Q or L-Q-C ....
  - ✓ Calculate and maximise profile likelihoods on 2,3 or more dimensions ...Not easy !
  - ✓ Or restrict analyses to subjects in dose-range where linear ...
    - But subjects will change between simulations
- The shape of the best fitting dose-response may actually vary in the different realisations
- The magnitude and possibly the shape of the dose response may be influenced by modifiers (ID)...

# Solution – choice of dose responses

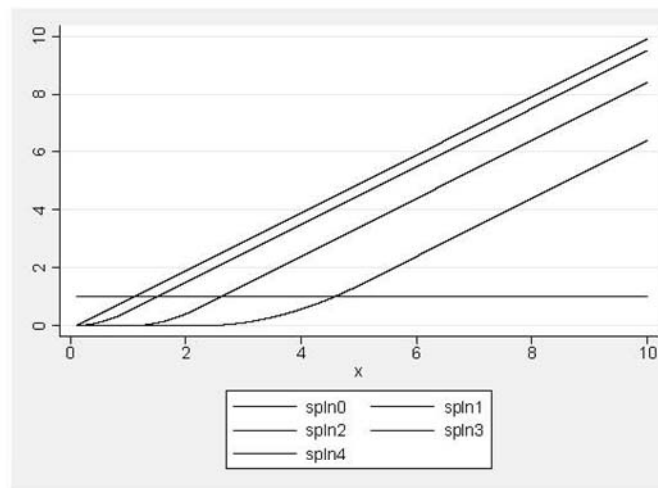
- Objective

- Use all the data
  - Avoid imposing a dose-response function that may not fit the data well
- ... and polynomials can provide very poor fit at extreme values, since data at small doses can strongly influence the predicted value at large doses*

*The work presented here is being conducted by Graham Byrnes (IARC)*

## Natural Quadratic Splines

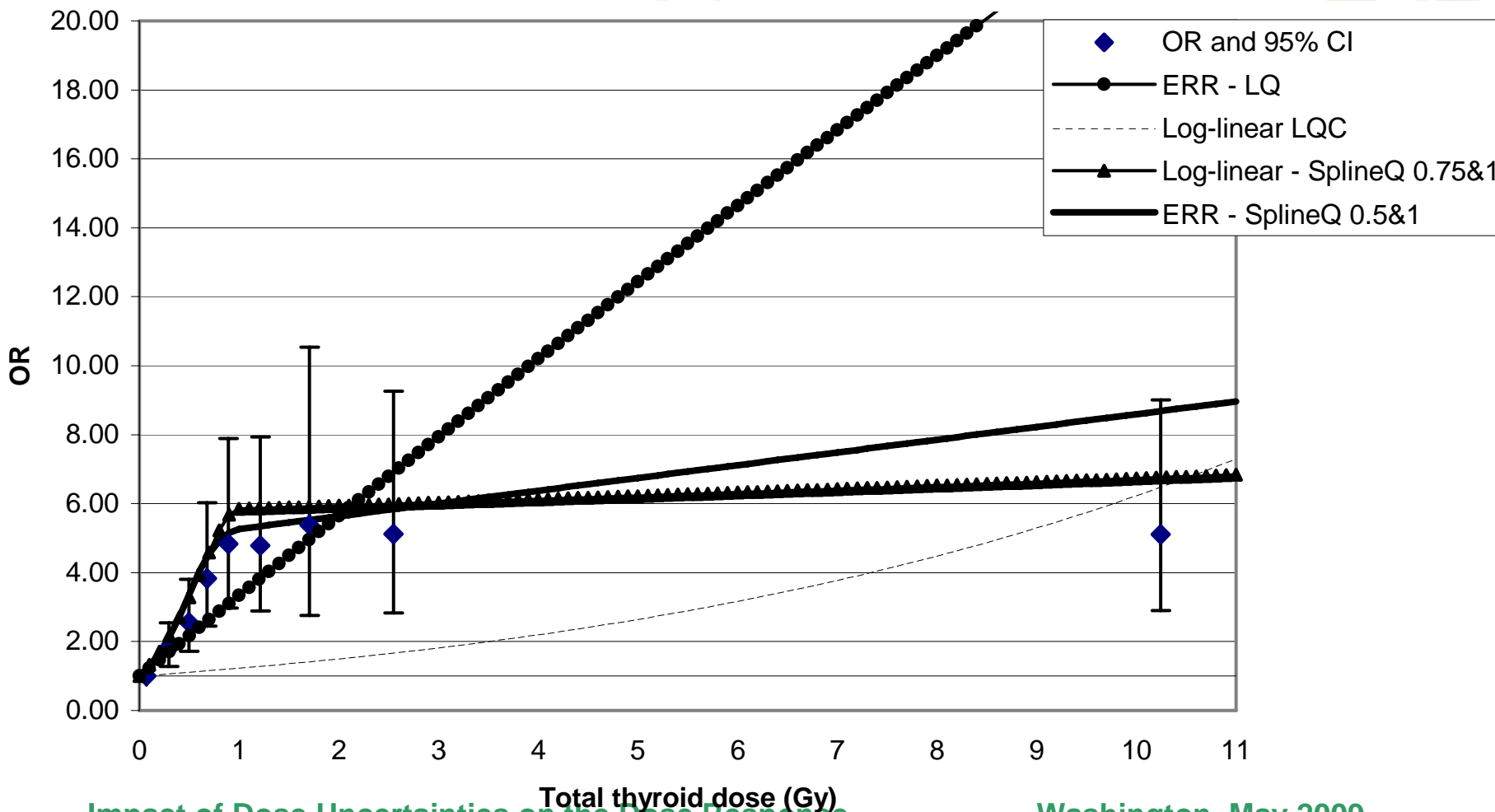
Any linear combination of the  $S_i$  will have continuous first derivatives





*Seem to predict qualitatively similar response curves  
regardless of the regression framework (ie logistic vs  
linear ERR, log-transformed or raw dose).*

**All studies**





# Solution - averaging of k-dimensional likelihood

- As an alternative method for k parameters (after trying a lot of things):
  - use the inverse Hessian at the MLE to obtain a preliminary variance-covariance matrix  $V$  ;
  - apply a coordinate transform (orthogonal transform followed by scaling) to map  $V$  to the identity matrix;
  - Define a  $(k - 1)$ -sphere in these coordinates, centered at the MLE, with radius  $\Phi^{-1}(1 - \alpha/2)$ . Conventionally, this would define the boundary of the 95% confidence set;
  - distribute points uniformly on the surface of the sphere (deterministically for  $k \leq 2$ , at random for  $k \geq 3$ );
  - adjust the radial position of each point, via 1-d Newton's method (with jump size limited to half or double the current radius) to achieve the appropriate difference of likelihood relative to the MLE.

# Parameter space to envelope of curves

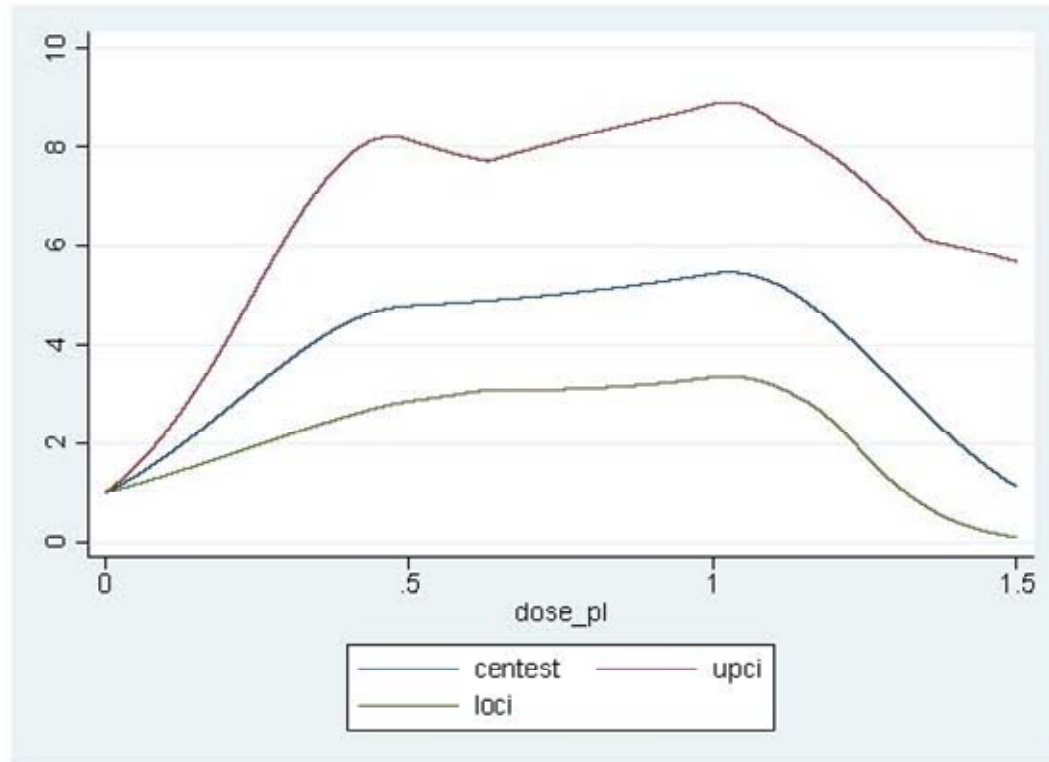
- The real goal is not to define the confidence set  $B$  in the parameter space, but to find the corresponding family of dose response curves

- For any give dose  $x$  and parameter vector  $\beta_1, \dots, \beta_k$ , the corresponding log odds-ratio curve has value

$$\Psi(x) = \sum_{j=1}^k \beta_j \cdot S_j(x)$$

- To find the boundary of the envelope of curves, we need to locate for each  $x$ , the  $\beta$  belonging to  $B$  which maximises or minimises  $\Psi(x)$ :
- Ideally this means locating the points on  $\partial B$  where the tangent space  $T \partial B$  is orthogonal to  $(S_1(x), \dots, S_k(x))$ .
- This is easy when the boundary is ellipsoidal, in general not.
- Practical solution: for each of the uniform boundary points, generate the corresponding curve; then for a set of doses, find the max and min among these curves.

# OR scale, restricted





# Where we are ...

- The approach can be implemented
- But:
  - width is based on the posterior likelihood having a chi-squared distribution ... **which appears not to be true...**
    - ✓ It is the log of the sum over the Monte-Carlo simulations of the *product* of the likelihoods from the conditionally independent case-control sets... *and the usual assumption of asymptotic normality fails.*
  - **confidence intervals appear to be too narrow ...**
    - ✓ and so are those in our previous 1-parameter analyses in nuclear workers and in liquidators ...
  - simulations currently being conducted to determine the distribution of the posterior likelihood