Epidemiological evidence for circulatory diseases – Occupational exposure

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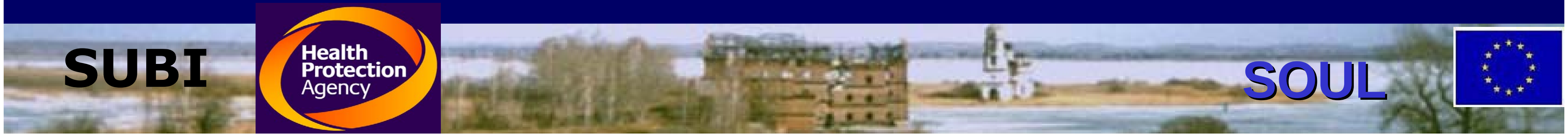
EU Scientific Seminar

Emerging evidence for radiation induced circulatory diseases

Luxembourg, 25 November 2008



Topics to be covered

- Summary of findings from occupational studies
- Limitations of these studies
- Background to the Mayak worker cohort and attributes of this study
- Main findings from Mayak workers on circulatory disease and radiation
- Comparison of the Mayak worker results with those from other occupational studies
- Future research needs

Studies of circulatory disease among radiologists and radiologic technologists

- Higher mortality among US radiologic technologists who started work early in the 20th century compared with those with started work later
  - *but less evidence of such a trend among UK and US radiologists (McGale & Darby, Radiat Res, 2005)*
- Mortality often less than expected from national rates
- Interpretation restricted by the lack of information on individual doses
  - *doses are now being reconstructed for US technologists*

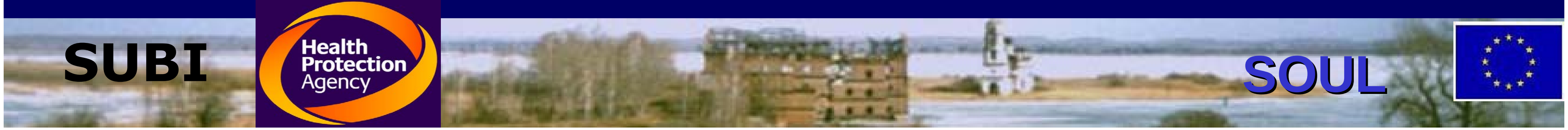
Radon-exposed miners

- Studies of circulatory disease mortality have given mixed results (UNSCEAR, 2006)

- By far the largest study was of 59,000 German uranium miners *(Kreuzer et al, Radiat Environ Biophys, 2006)*
  - *This showed no association with cumulative exposure to radon, external gamma radiation or long-lived radionuclides*
  - *Doses to the heart and arteries are likely to have been low (roughly <100 mSv on average)*
  - *No information on potential confounders*

Nuclear industry workers: international

- Vrijheid *et al* (*Int J Epidemiol, 2007*) examined non-cancer mortality among 275 000 workers from 14 countries
- Findings were consistent both with no raised risk and with a risk of the size seen in the LSS
- The low statistical power of this analysis reflected
  - *The relatively short follow-up (average age at end of follow-up was 46 years)*
  - *Relatively low mean dose (20.7 mSv)*
- Study excluded workers with potential internal exposures



Nuclear industry workers: BNFL (UK)

- McGeoghegan *et al* (*Int J Epidemiol, 2008*) examined non-cancer mortality among about 42 000 radiation workers
- Longer follow-up and higher mean external dose (53.0 mSv) than in the international study
- Included workers with internal exposures, but analysis focussed on external doses
- Mortality from circulatory disease and from non-cancer causes combined was less than expected from rates for north-west England

Trend with external dose in circulatory disease mortality among BNFL workers

	Excess relative risk, ERR per Sv (90% CI)
All radiation workers	0.65 (0.31, 1.05)
Sub-groups of workers:	
Industrial, external	*1.25 (0.44, 2.25)*
Non-industrial, external	*1.38 (-0.28, 3.70)*
*Industrial, internal**	*0.76 (0.30, 1.32)*
Non-industrial, internal	*-0.29 (<-0.73, 0.33)*

**Ever monitored for internal exposure*

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Problems with interpretation of occupational studies of circulatory disease

Potential for bias or confounding

- "Healthy worker effect" complicates comparisons with national mortality rates
- Usually based on mortality data
  - *potential for misclassification of specific disease types*
- Generally lack information on known risk factors for circulatory disease
  - *eg. smoking, alcohol consumption*

Problems with interpretation of occupational studies of circulatory disease (continued)

Low statistical power

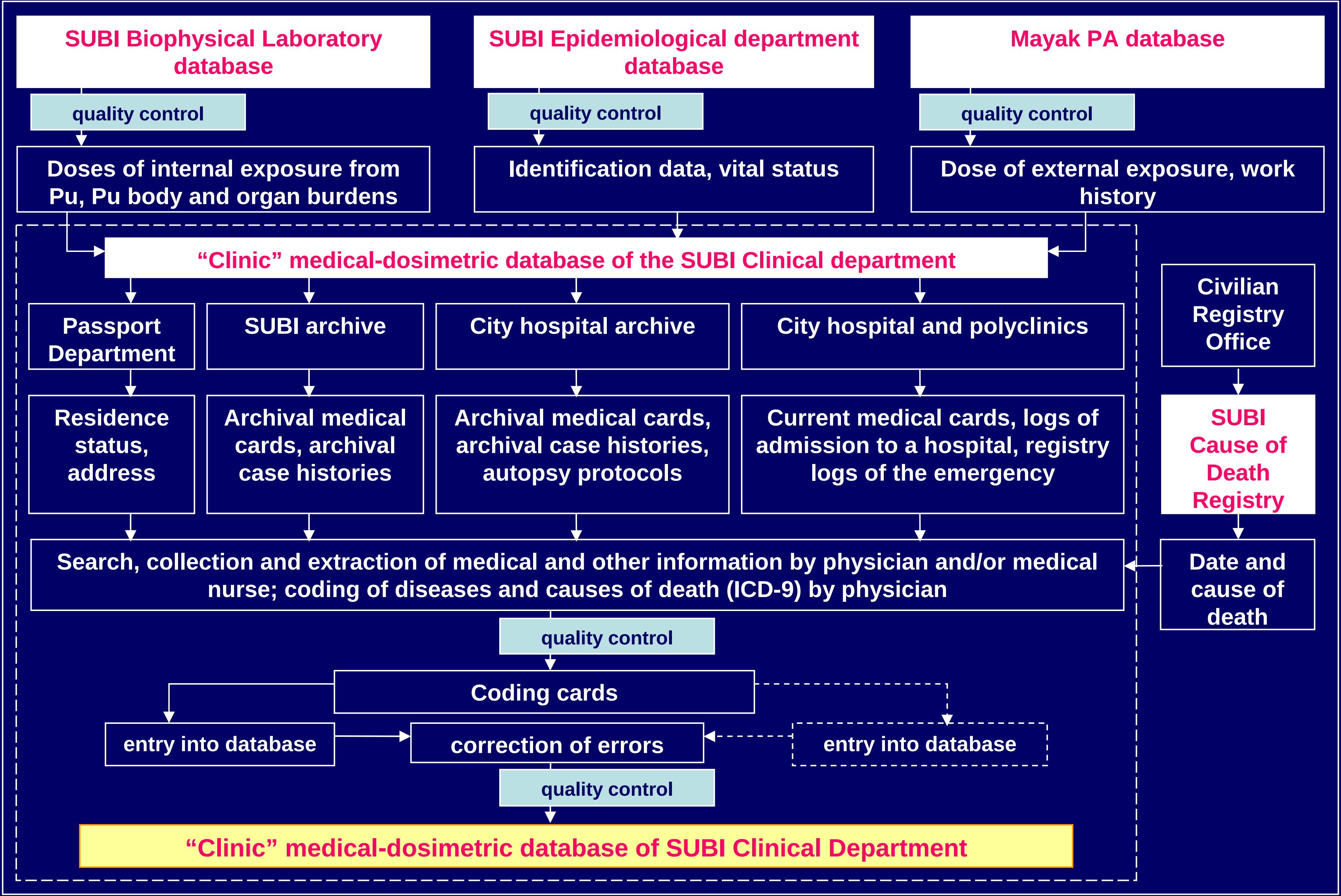
- Many studies restricted in terms of cohort size, length of follow-up and/or range of doses
- LSS suggests that raised risk of circulatory disease is lower – in relative terms – than that for cancer
  - *less than 10% increase for doses below 0.5 Sv*
- However, important to recognise that, because circulatory disease is so common, a small relative risk may represent an absolute excess risk similar to that for cancer

The first Russian nuclear facility – Mayak Production Association – started operation in June 1948. Mayak PA is located 10 km from Ozyorsk city in the Southern Urals.

"Mayak" PA:

- Production reactors
- Radiochemical plant
- Plutonium plant
- Auxiliary plants

Collection of primary data



T.V Azizova et al. The "Clinic" medical-dosimetric database of Mayak production association workers: structure, characteristics and prospects of utilization. Health Phys 94, 449-58 (2008).

Structure of the "Clinic" medical dosimetric database

Mayak worker cohort

Identification number

Passport data

- Surname, name, patronymic name
- Gender
- Date of birth
- Nationality
- Education

Medical history and vital status

- Date of pre-employment examination
- Date of "last medical information"
- Vital status
- Residence status (Ozyorsk resident or migrant)
- Date of death
- Cause of death
- Autopsy data

Initial state of health

Smoking history

Alcohol consumption history

Clinical data

All workers

- Morbidity data
- Peripheral blood
- Blood pressure
- Body mass

Selected workers

- Bone marrow
- Cytogenetic analysis
- Biochemical analysis of blood
- Respiratory function
- Roentgenography of lungs

Patients with Acute Radiation Syndrome (ARS)

- Symptoms and signs
- Treatment

Patients with Chronic Radiation Sickness (CRS)

- Symptoms and signs
- Treatment

Patients with plutonium pneumosclerosis (PuPn)

- Symptoms and signs
- Treatment

Workers with Local Radiation Injuries (LRI)

- Localization
- Severity degree
- Symptoms and sings
- Treatment

Expert review and verification of diseases and deterministic effects

Reproduction

Females

- Characteristics of reproductive cycle
- Pregnancies and their outcomes

Families

- Wife
- Husband
- Children

Work history

- Date of starting work
- Date of stopping work
- Place of employment
- Occupation

Dosimetry data

All workers

External gamma and neutron exposure

- Shift doses
- Monthly doses
- Annual doses
- Absorbed doses to organs

Internal exposure from incorporated plutonium-239

- Body burden
- Monthly and annual absorbed doses to organs

ARS patients

- Accident doses (gamma and neutron exposure)
- Duration of acute exposure

Preconception doses

Doses during pregnancy

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Southern Urals Radiation Risk Research (SOUL)

– supported by the European Commission's 6th Framework Programme (Euratom) and the Federal Medical Biological Agency (Russian Federation)

Work Package 2.4: Research objective

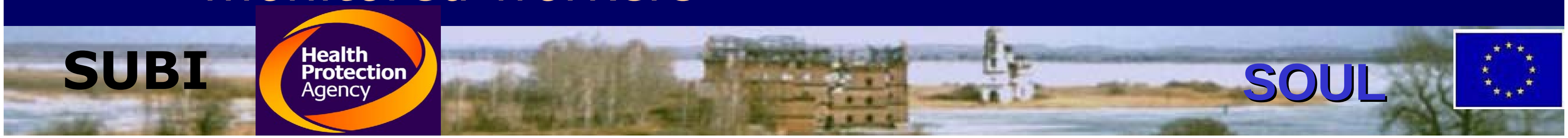
- To estimate risks of morbidity and mortality from circulatory diseases up to the end of 2000 in the cohort of workers first employed at the main facilities of Mayak PA in 1948-1958 in relation to external and internal radiation, whilst allowing for age, gender and non-radiation risk factors

Characteristics of the cohort of Mayak workers first employed in 1948-1958

Characteristic	Number	%
Workers included in the cohort	12210	100.0
Females	3552	29.1
Migrants from Ozyorsk	6557	53.7
Vital status known	10789	88.4
Died	5685	52.7
Died in Ozyorsk	3009	52.9
Autopsy performed	1948	34.3
Autopsy performed in Ozyorsk	1868	95.9
Cause of death known	5317	93.5
Alive as of 31 December 2000	5104	47.3
Alive and lived in Ozyorsk as of 31 December 2000	2548	49.9
Medical documentation (morbidity data) available	11597	95.0

Radiation monitoring

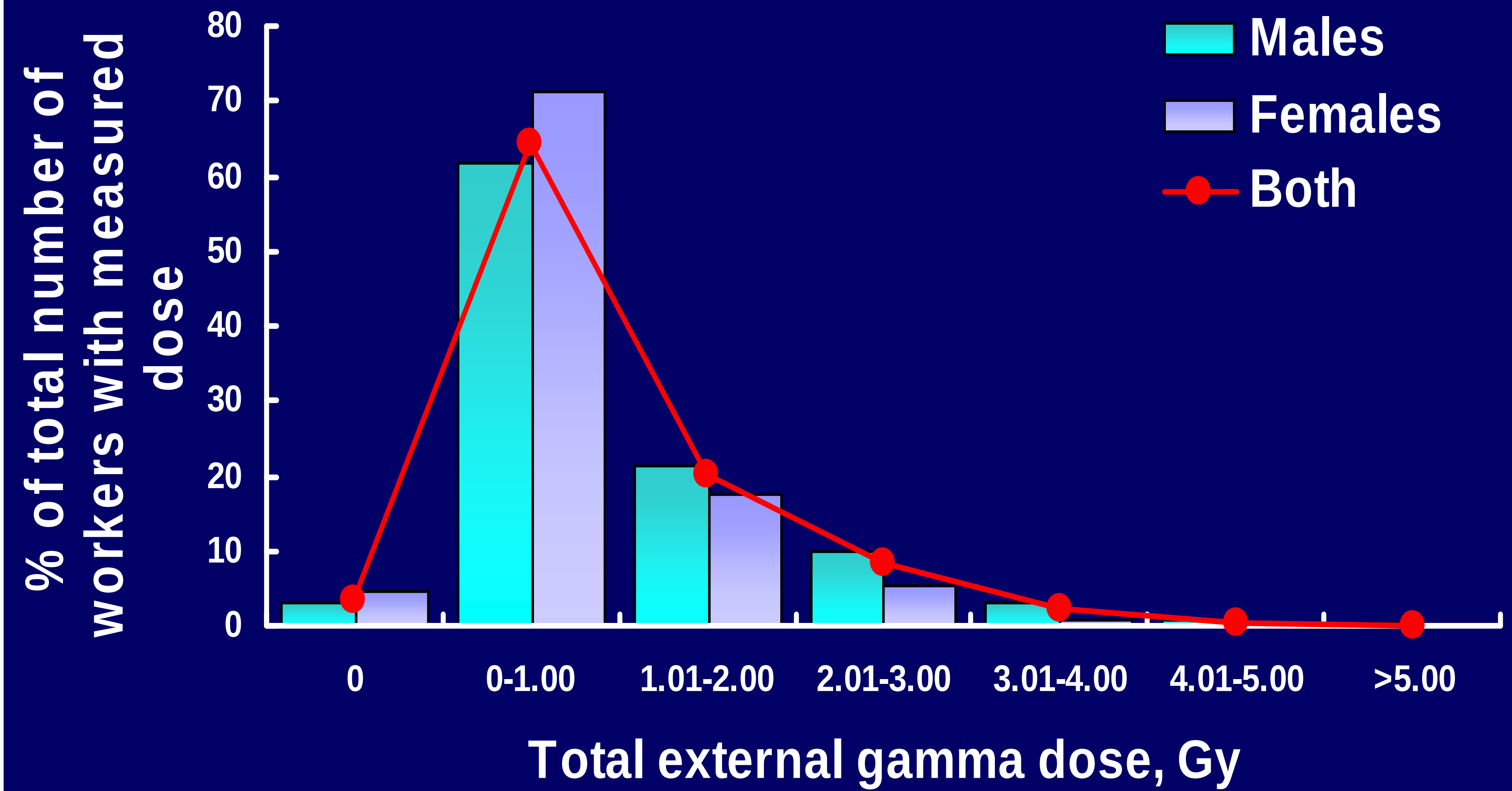
- Individual monitoring of exposures to external gamma doses was conducted from the beginning of operations at Mayak
  - *Annual external gamma doses are available for 99.9% of workers in the study cohort*
- Regular monitoring of internal exposure among those who worked with transuranium radionuclides began later, during the 1960s
- Plutonium body burden was measured (and estimates of internal doses were subsequently derived) only for 30% of workers who were in contact with transuranium radionuclides
  - *Analyses of internal exposures are restricted to monitored workers*



Dosimetry (*Mayak Doses 2005*)

Exposure	Average total dose ± SE (range), Gy
External gamma	
males	0.91±0.01 (0-5.92)
females	0.65±0.01 (0-5.70)

Distribution of workers in the study cohort by total external gamma dose



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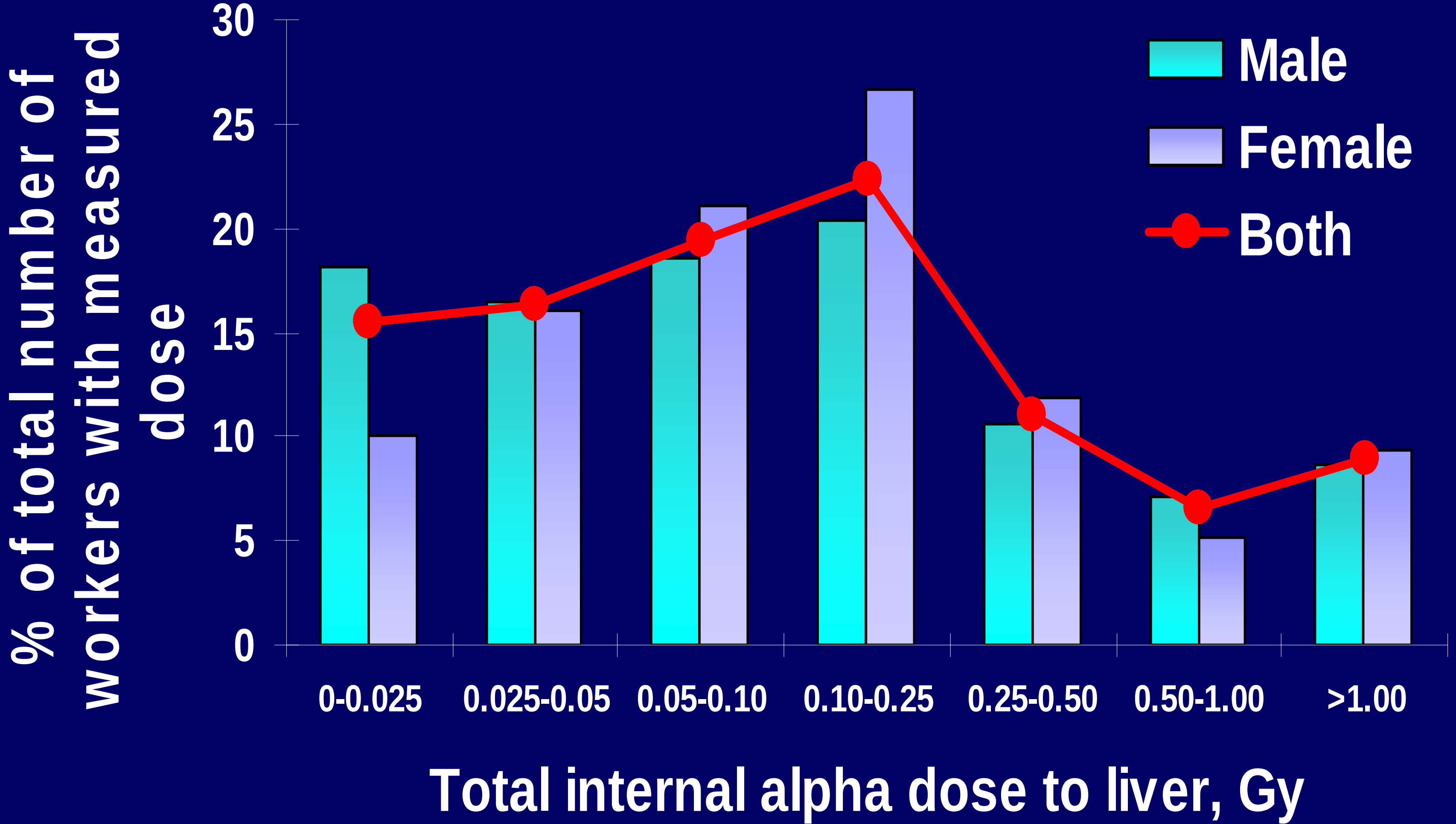
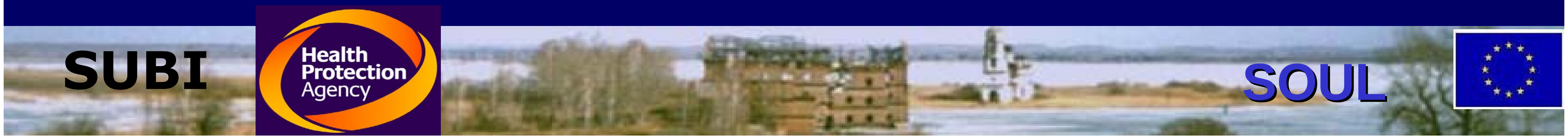
Dosimetry (*Mayak Doses 2005*)

Exposure	**Average total dose ± SE (range), Gy**
Internal alpha (Pu-239, liver)	
males	0.40±0.02 (0-17.90)
females	0.81±0.13 (0-127.82)

- Liver dose used as surrogate for dose to blood vessels/heart - *these doses would differ but they should be highly correlated*

Distribution of workers in the study cohort with measured plutonium body burden by total liver dose from internal alpha exposure to Pu-239





Quality control

- Conducted on a regular basis
- For this analysis, specific checks were conducted on:
  - *identification of the worker cohort*
  - *dosimetry*
  - *non-radiation risk factors*
  - *follow-up*
- These checks showed a high level of data accuracy and completeness

Examples of quality control findings

- Level of data loss was only about 2.5%
- Expert reviews of samples of circulatory diseases diagnosis showed high levels of diagnostic verification (98.8% for acute myocardial infarction and 94.9% for stroke)
- Estimated that only 1.7% of cases of circulatory diseases were missed in the database
- Comparison of smoking and alcohol consumption data from different sources showed good agreement (93 - 95%)
- Errors identified were corrected

Period of follow-up

Start of follow-up

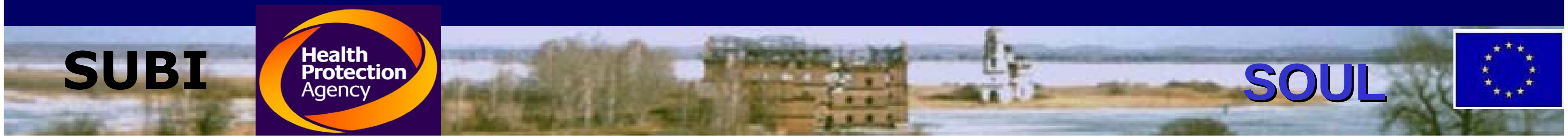
- Date of first employment at one of the main plants of Mayak PA

End of follow-up The earliest of:

- Date of first diagnosis of circulatory disease (*for morbidity analysis*);
- Date of death;
- 31 December 2000;
- Date of migration from Ozyorsk (*for morbidity analysis*);
- Date of last known vital status.

Effects studied

- Ischemic heart disease (<u>IHD</u>; ICD9: 410-414)
- Cerebrovascular disease (<u>CVD</u>; ICD9: 430-438)



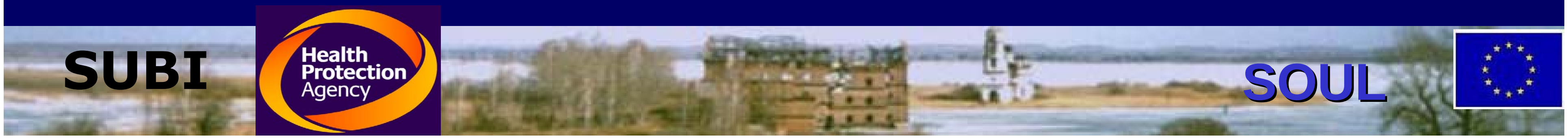
Numbers of deaths or cases and corresponding numbers of person-years for analyses of risks of circulatory disease morbidity and mortality

	Number of cases	Number of person-years
Mortality - IHD	1495	443350
Mortality - CVD	753	443350
Morbidity - IHD	3751	205249
Morbidity - CVD	4418	197344

Analyses of non-radiation risk factors

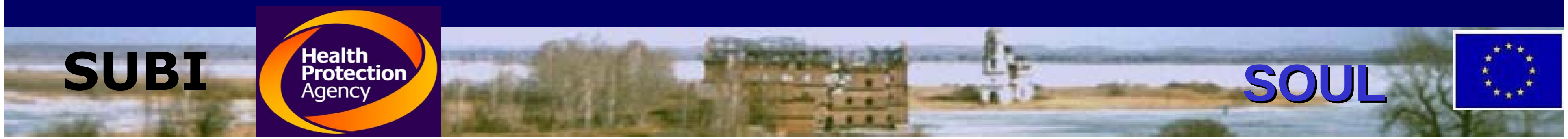
Increased risks of morbidity and mortality from circulatory diseases were found in the study cohort in relation to:

- Gender
- Age
- Hypertension
- Increased body mass index
- Smoking



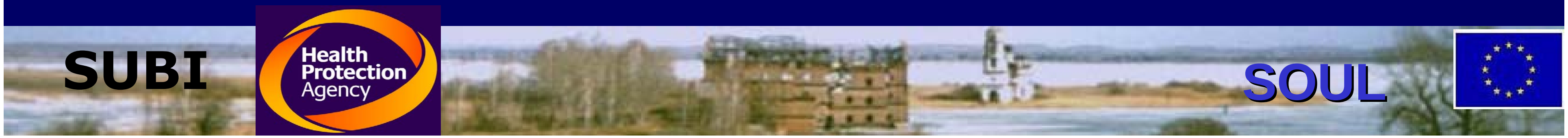
Methods for analysing radiation risks

- Relative risks were calculated for categories of external/internal dose, having adjusted for non-radiation factors via stratification
- Trends in relative risk with dose (excess relative risk per Gy, ERR/Gy) calculated using a similar approach
- Sensitivity analyses considered impact of adjusting for additional factors and using different lag periods
- Effect modification was considered by considering sub-groups of workers

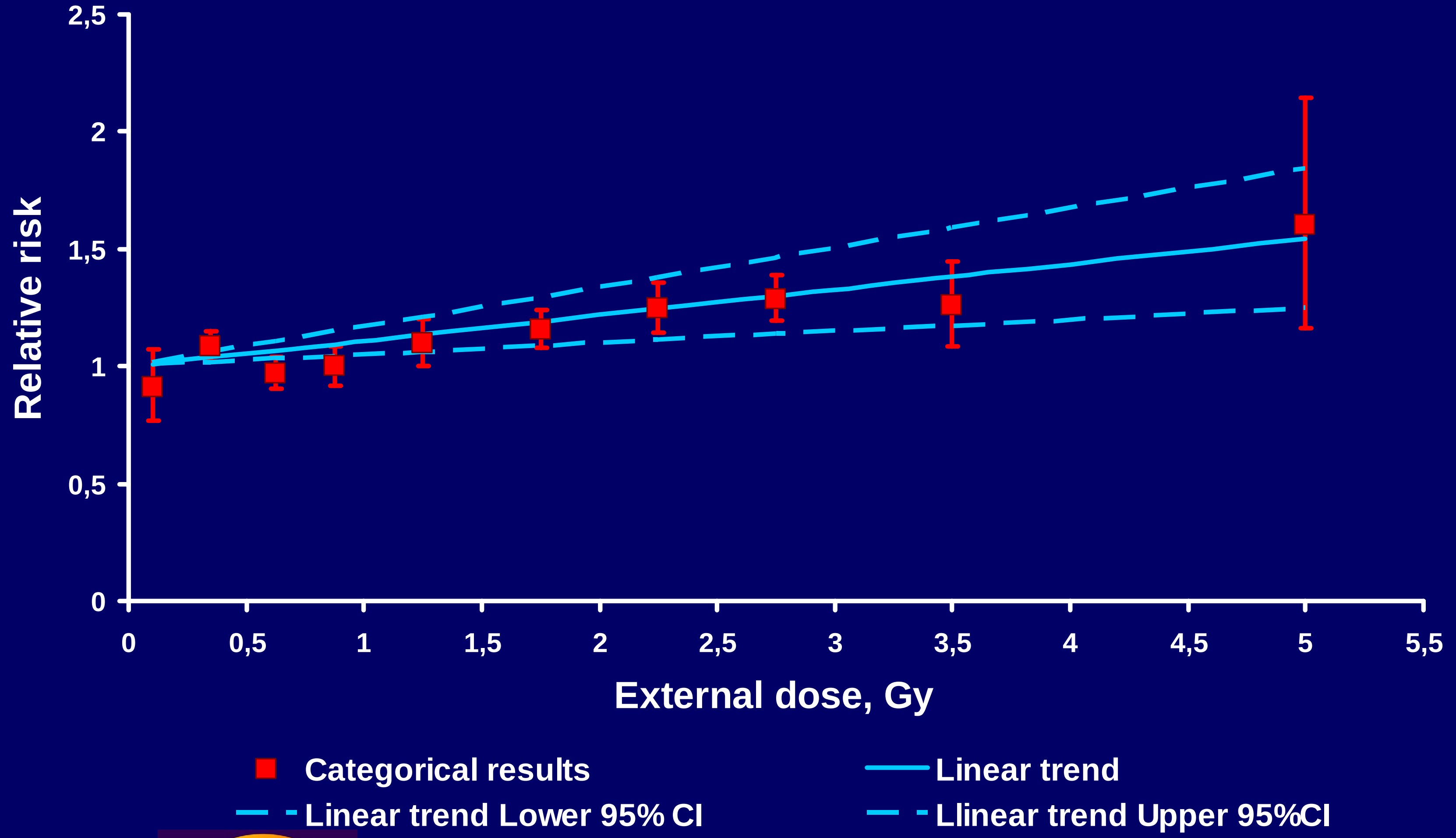


Relative risk & 95% CI for analyses of external dose

	IHD (vs. <0.5 Gy)	
	0.5 - 1.0 Gy	> 1.0 Gy
Mortality	0.92 (0.78, 1.08)	1.11 (0.96, 1.30)
Morbidity	1.02 (0.92, 1.13)	1.20 (1.09, 1.32)
	CVD (vs. <0.5 Gy)	
	0.5 - 1.0 Gy	**> 1.0 Gy**
Mortality	1.15 (0.92, 1.43)	0.99 (0.80, 1.24)
Morbidity	1.14 (1.04, 1.25)	1.60 (1.47, 1.75)



ERR/Gy & 95% CI for analyses of external dose
IHD (morbidity)
ERR/Gy = 0.109 (0.049-0.168)



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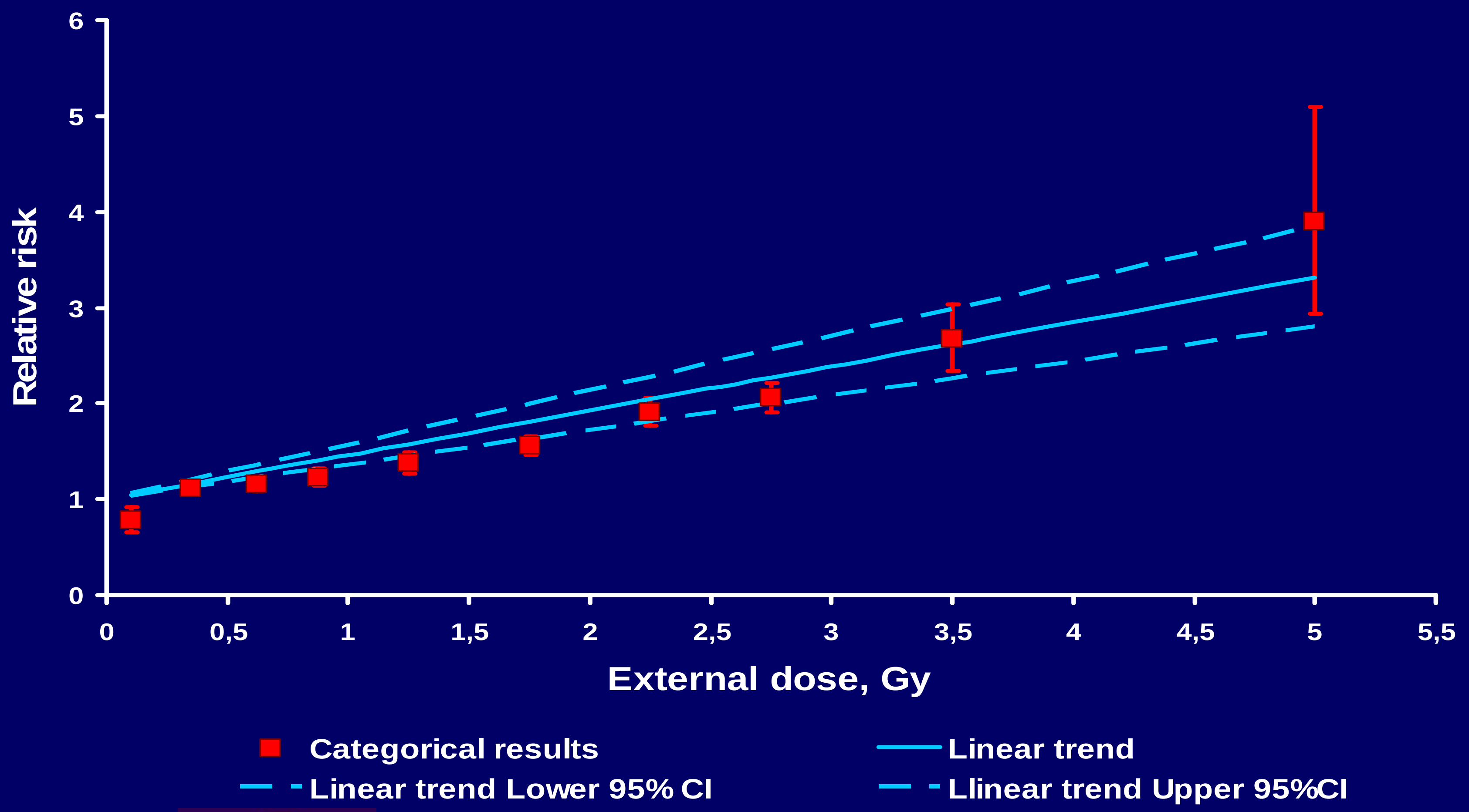
ERR/Gy & 95% CI for analyses of external dose

CVD (morbidity)

ERR/Gy = 0.464 (0.360-0.567)



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Sensitivity analyses and effect modification for external dose analyses

- Findings for IHD morbidity and CVD morbidity did not vary greatly when:
  - *adjusting for extra non-radiation factors;*
  - *adjusting for internal dose;*
  - *using different lag periods*
- Raised risk of IHD morbidity seen mainly in males, but findings were consistent across genders
- Raised risk of CVD morbidity seen in both genders:

  ERR/Gy = 0.39 (0.28-0.52), males

  = 0.71 (0.44-0.97), females

Relative risk & 95% CI for analyses of internal liver dose

	IHD (vs. <0.1 Gy)	
	0.1- 0.5 Gy	> 0.5 Gy
Mortality	1.33 (1.08, 1.64)	1.59 (1.16, 2.19)
Morbidity	1.17 (1.06, 1.30)	1.23 (1.04, 1.45)
	CVD (vs. <0.1 Gy)	
	0.1- 0.5 Gy	> 0.5 Gy
Mortality	1.40 (1.02, 1.92)	1.05 (0.61, 1.80)
Morbidity	1.23 (1.13, 1.35)	1.58 (1.35, 1.85)

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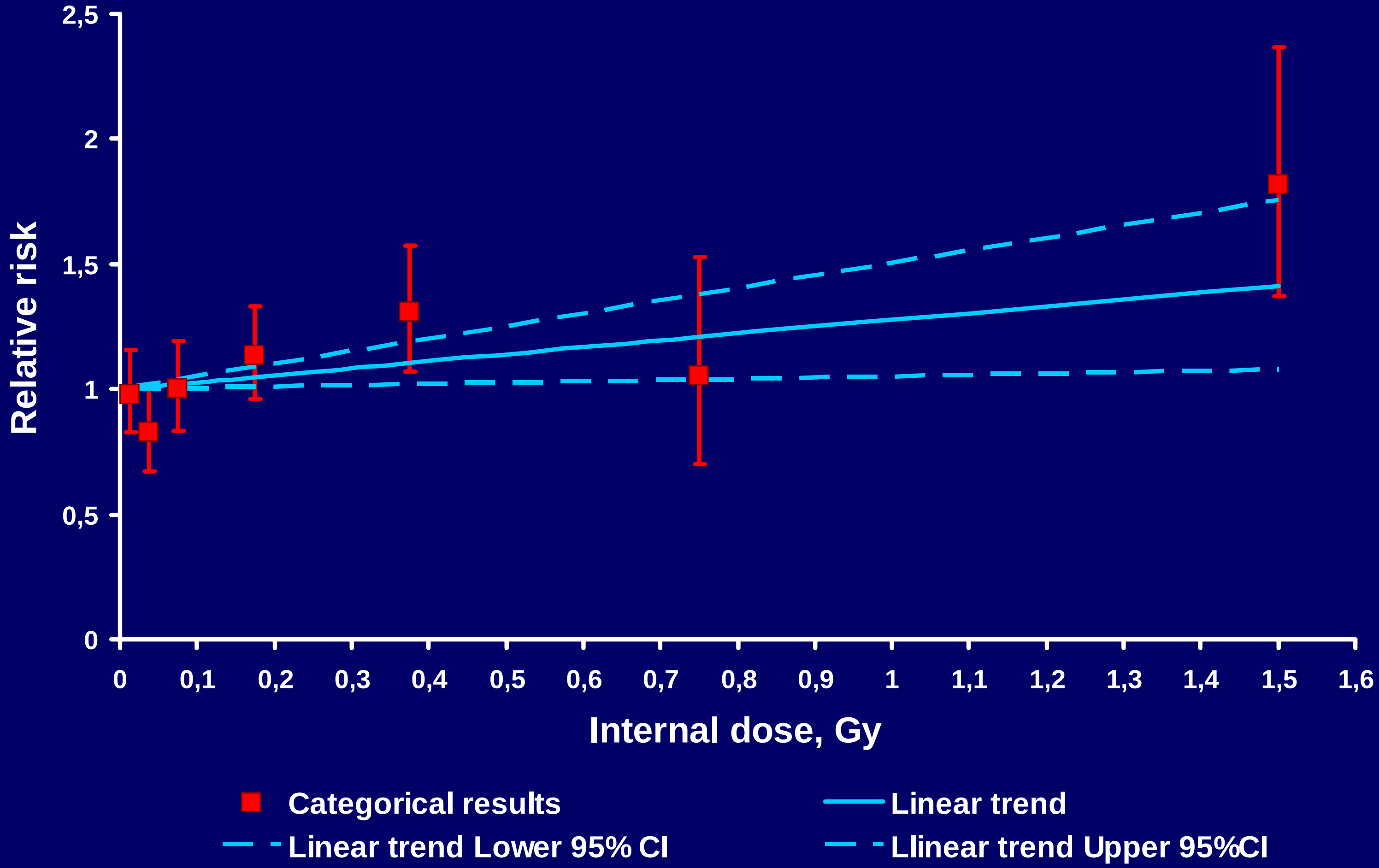
ERR/Gy & 95% CI for analyses of internal liver dose

IHD (mortality)

ERR/Gy = 0.275 (0.050-0.501)



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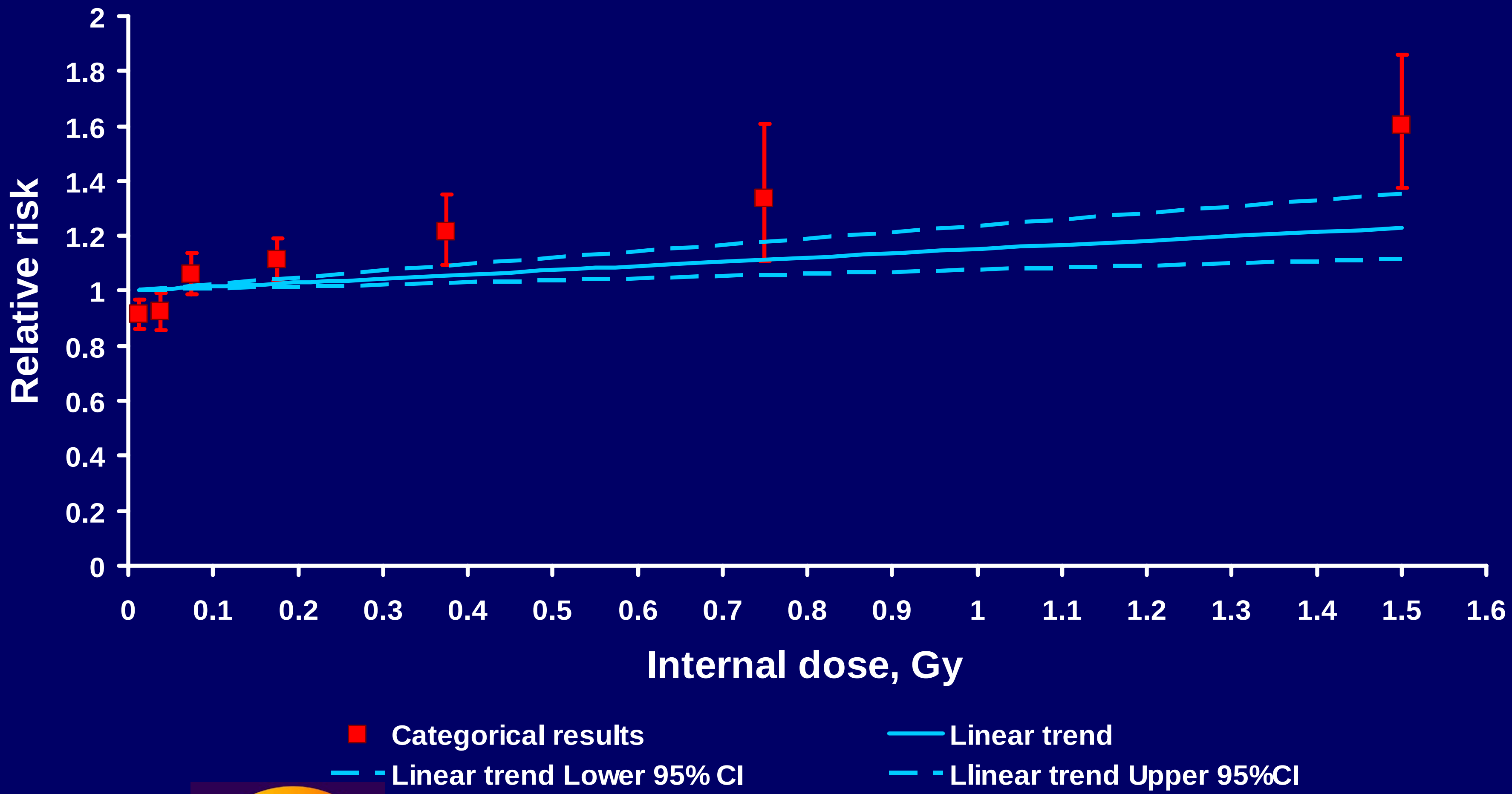
ERR/Gy & 95% CI for analyses of internal liver dose
CVD (morbidity)
ERR/Gy = 0.155 (0.075-0.235)



Sensitivity analyses and effect modification for internal dose analyses

IHD mortality

- Little change in results when adjusting for extra non-radiation factors or using different lag periods
- However, ERR/Gy is lower and not statistically significant after adjusting for external dose

CVD morbidity

- Little change in results when adjusting for extra non-radiation factors **or for external dose**
- ERR/Gy increases with increasing lag period
- Raised risks seen separately among workers at the radiochemical plant and at the plutonium plant

Comparison of IHD findings from various studies of external exposure

Cohort	Mean cumulative dose (Gy)	Mortality or *morbidity*?	No. of deaths or cases	ERR/Gy
Japanese A-bomb survivors:				
LSS	0.20	Mortality	4,477	0.17 (90% CI 0.08, 0.26)
Adult Health Study	0.57	*Morbidity*	1,546	0.05 (95% CI -0.05, 0.16)
Mayak workers	0.84	Mortality	1,495	0.07 (95% CI -0.02, 0.15)
Mayak workers	0.84	*Morbidity*	3,751	0.11 (95% CI 0.05, 0.17)
Nuclear workers (international)	0.018	Mortality	5,821	-0.01 (95% CI -0.59, 0.69)
BNFL workers (UK)	0.053	Mortality	3,567	0.70 (90% CI 0.33, 1.11)
Chernobyl recovery operations workers (Russia)	0.109	*Morbidity*	10,942	0.41 (95% CI 0.05, 0.78)

Comparison of CVD findings from various studies of external exposure

Cohort	Mean cumulative dose (Gy)	Mortality or *morbidity*?	No. of deaths or cases	ERR/Gy
Japanese A-bomb survivors:				
LSS	0.20	Mortality	3,954	0.12 (90% CI 0.02, 0.22)
Adult Health Study	0.57	*Morbidity*	729	0.07 (95% CI -0.08, 0.24)
Mayak workers	0.84	Mortality	753	-0.02 (95% CI -0.12, 0.07)
Mayak workers	0.84	*Morbidity*	4,418	0.46 (95% CI 0.36, 0.57)
Nuclear workers (international)	0.018	Mortality	1,224	0.88 (95% CI -0.67, 3.16)
BNFL workers (UK)	0.053	Mortality	1,018	0.43 (90% CI -0.10, 1.12)
Chernobyl recovery operations workers (Russia)	0.109	*Morbidity*	12,832	0.45 (95% CI 0.11, 0.80)

Conclusions of Mayak analysis

- Raised risks of circulatory disease have been found in relation to:
  - *external radiation dose*, having adjusted for non-radiation factors and internal dose, and
  - *internal radiation dose*, having adjusted for non-radiation factors and (in the case of CVD morbidity) for external dose
- Risk estimates for external radiation are generally compatible with those from other large occupational studies and for the A-bomb survivors

Future research needs

- More powerful information on the effects of protracted exposures at lower doses, whilst allowing for non-radiation factors

- Among Mayak workers, this topic is currently being addressed by:
  - *expanding the cohort to include workers employed after 1958, who tended to receive lower doses than earlier workers*
  - *extending the period of follow-up until 31 December 2005*
  - *considering diagnostic medical exposures*

Acknowledgements

- European Commission
- Federal Medical Biological Agency of the Russian Federation