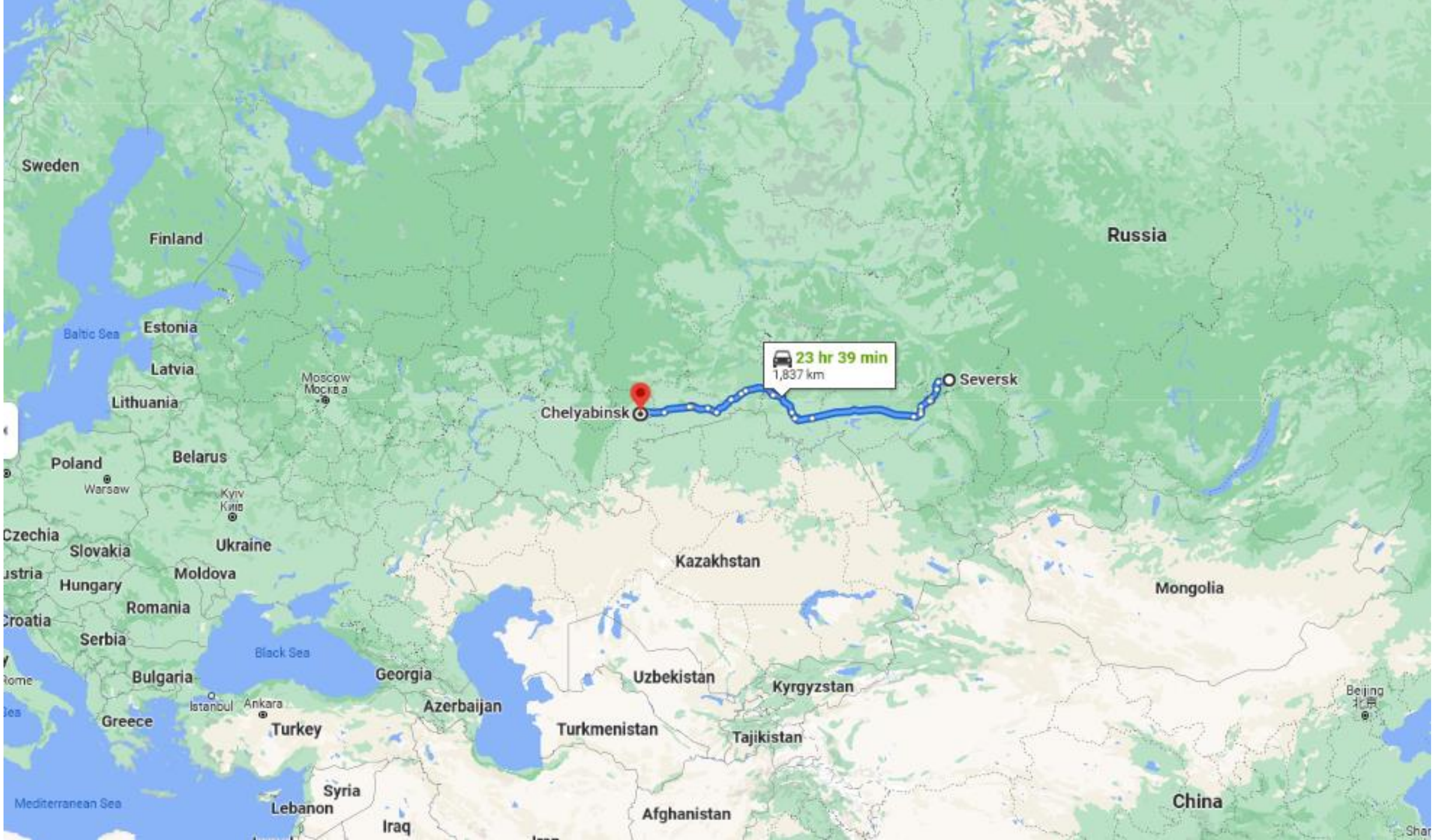
Future Opportunities:

Seversk Pilot Study

ICRP WORKSHOP
"30 Years of Scientific Achievements for International Radiological Protection: Summary of the Southern Urals Health Studies Program"

MAY 24-25, 2024 Vienna, Austria

Lydia B. Zablotska, MD, PhD
S.P. Lucia Professor of Preventive Medicine and Epidemiology, UCSF


23 hr 39 min
1,837 km
Chelyabinsk
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Czechia
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Hungary
Moldova
Romania
Croatia
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Istanbul
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Turkey
Azerbaijan
Kazakhstan
Uzbekistan
Kyrgyzstan
Turkmenistan
Tajikistan
Mongolia
Beijing
Syria
Lebanon
Iraq
Afghanistan
China
Mediterranean Sea

History of the Seversk Pilot Study

- **On May 10-15, 2014**, the Joint Coordinating Committee for Radiation Effects Research (**JCCRER**), established within the framework of the Agreement between the Government of the United States of America and the Government of the Russian Federation on Cooperation in Research on Radiation Effects for the Purpose of Minimizing the Consequences of Radioactive Contamination on Health and the Environment dated 14.01.1994, the scientific review group (**SRG**) **visited the Seversk Biophisical Research Center (SBR Center**).
- The staff of the **SBR Center** provided comprehensive answers to all questions, as well as demonstrated all information and research resources, which allowed the **SRG to verify the availability, reliability and completeness of available data** on possible **biomedical radiogenic effects**.
- The members of the **SRG** delegation noted in their summary report that **98%** of the information available in the SBR Center was related to **low doses** of ionizing radiation, and that the **vital status** of workers has been verified by more than **80%.**
- Following the visit, the SRG recommended to **include the SBR in** the framework of studies conducted by the **JCCRER**.

SBR Center & iPAUW

- In 2020, the SBR Center was invited to participate in i***nternational Pooled Analysis of Uranium Processing Workers*** ***(*****IPAUW**).
- In 2021, a Data transfer Agreement was signed between the University of San Francisco and the SBR Center, agreed with the FMBA of Russia and the Rosatom State Corporation (SGCE).
- Seversk cohort profile paper published in IJRB (Karpov et al. 2021).
- Seversk participation in iPAUW suspended in February 2022.

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Descriptive characteristics of occupational exposures and medical follow-up in the cohort of workers of the Siberian Group of Chemical Enterprises in Seversk, Russia

Andrey B. Karpov, Ravil M. Takhauov, Andrey G. Zerenkov, Yulia V. Semenova, Igor M. Bogdanov, Svetlana B. Kazantceva, Aleksey P. Blinov, Dmitriy E. Kalinkin, Galina V. Gorina, Olesya V. Litvinova, Yuriy D. Ermolaev, Elena B. Mironova, Mikhail B. Plaksin, Anas R. Takhauov & Lydia B. Zablotska

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Siberian Group of Chemical Enterprises (SGCE)

- Seversk is a **closed city in Tomsk Oblast**, Russia, located 9 miles northwest of Tomsk and has a population of about ~ **100,000**. Previously named Tomsk-7 (accident on April 6, 1993).
- Seversk is the site of the Siberian Chemical Combine (SCC), founded in 1954 (first operations started in 1949, critical in 1950). It comprises several nuclear reactors and chemical plants for separation, enrichment, and reprocessing of uranium and plutonium.
  - "SCC integrates high radiation and nuclear hazard industries and facilities, engaged in the development, production, operation, storage, transportation, utilization of nuclear weapons and radiation-hazard materials and goods."
- Following an agreement in March 2003 between Russia and the United States to shut down Russia's three remaining plutonium-producing reactors, two of the three plutonium producing reactors (the two that are situated in Seversk, at the Sibirskaya Nuclear Powe Plant) were shut down.
- Currently referred to as SGCE – Siberian Group of Chemical Enterprises (SGCE).

Seversk Pilot Study Specific Aims

1. To estimate doses to the lungs from uranium and plutonium internal exposures in the SGCE Uranium subcohort.
2. To conduct dose-response analyses of lung cancer incidence and mortality due to radiation doses to the lungs from external and internal occupational radiation exposures in the SGCE Uranium subcohort.
3. To conduct dose-response analyses of incident solid cancers other than lung, liver and bone in relation to external irradiation in the SGCE full cohort.

Methods

- **Individual gamma radiation exposures were derived from workplace badge measurements.**
- **Individual doses from internal exposures as well as exposures from other work-related physical and chemical agents could be estimated.**
  - Systematic monitoring of plutonium and uranium alpha-emitting radio nuclides in the SGCE employees was initiated in early 1960s by specialized biophysical laboratory using the indirect method based on the radiochemical analysis of biological samples.
- **Passive and active follow-up:**
  - Passive follow-up was done through linkage of the employment roster with various local databases, e.g., offices of vital status registration in Seversk and other cities of the Tomsk oblast, employment office at the SGCE, local hospital in Seversk and its associated outpatient clinic (the only medical facility in the area), police database and address bureau.
  - Active follow-up was conducted by calling all available phone numbers several times.
  - For those workers who have not been found in any of the databases or through active follow-up after ending their employment, it was assumed that workers have moved out of the catchment area and the last date of known alive was listed as the last day of employment.

The System of Health Care For Seversk Population

- Non-cancer outcomes: thyroid diseases, AMI, osteoporosis

- Data coded using ICD-10 classification

Seversk Clinical Hospital was founded in 1951

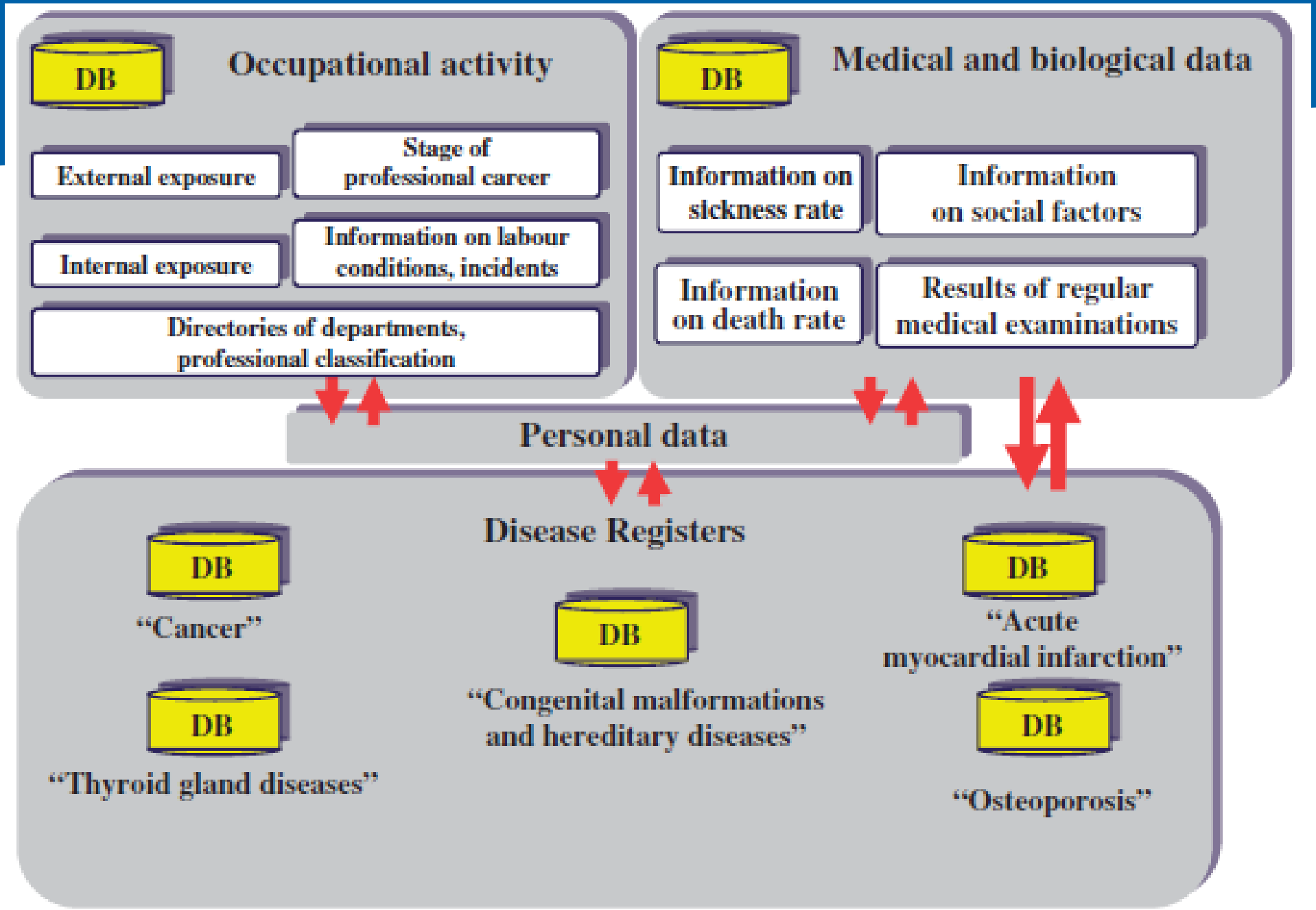

DB
Occupational activity
External exposure
Stage of professional career
Internal exposure
Information on labour conditions, incidents
Directories of departments, professional classification
DB
Medical and biological data
Information on sickness rate
Information on social factors
Information on death rate
Results of regular medical examinations
Personal data
Disease Registers
DB
"Cancer"
DB
"Thyroid gland diseases"
DB
"Congenital malformations and hereditary diseases"
DB
"Acute myocardial infarction"
DB
"Osteoporosis"

Table 1. Descriptive characteristics of the Seversk cohort, (first employed 1950-2010, followed up 1950-2018).

Category		Details
Total		64,949
Females, n (%)		15,913 (24.5)
Still employed in 2018, n (%)		3,333 (5.1)
Employment duration, years, mean, median (range)		15.2, 10.6 (0-59.9)
Follow-up duration, years, mean, median (range)		25.9, 26.7 (0-67.3)
Age start of employment, years, mean, median (range)		24, 22 (14-74)
Age end of follow-up, years, mean, median		59, 60
Facility	Enrichment	6,442 (9.9)
	Plutonium	9,726 (15.0)
	Reactor	7,974 (12.3)
	Radiochemical	6,243 (9.6)
	Sublimation	4,593 (7.1)
	Support Facility	29,971 (46.2)
Birth cohort	1889-1919	1,302 (2.0)
	1920-1939	19,463 (30.0)
	1940-1959	28,972 (44.6)
	1960-1979	12,733 (19.6)
	1980-1993	2,479 (3.8)

Table 1. Descriptive characteristics of the Seversk cohort (first employed 1950-2010, followed up 1950-2018), *cont'ed*.

Category		Details
Smoking, n (%)	Ever	1,596 (2.5)
	Never	17,151 (26.4)
	Missing	46,202 (71.1)
"Social status", n (%)	Blue collar	51,654 (79.5)
	White collar	13,107 (20.2)
	Other (military, student, retired, farm worker, unknown/missing)	188 (0.3)
Education	Less than high school	14,272 (22.0)
	High school	9,211 (14.2)
	Professional	29,744 (45.8)
	College	11,144 (17.2)
	Post-graduate	82 (0.1)
	Unknown	496 (0.8)

Table 2. Characteristics of the Seversk cohort workers, by plant.

Plant	Start date of activity	Number of workers	Monitored for external exposure[a]	Monitored for internal exposure[a]
Enrichment	1953	6,431	1424 (22.1%)	755 (11.7%)
Plutonium	1961	9,666	3,904 (40.4%)	4315 (44.6%)
Reactor	1955	8,002	5907 (73.8%)	–
Radiochemical	1961	6,232	5227 (83.8%)	2307 (37.0%)
Sublimation	1954	4,586	2335 (50.9%)	1198 (26.1%)
Subtotal all plants	1954-1961	34,917	18,797 (53.8%)	8,575b (24.6%)
Support Facility	1954-1961	30,017	3058 (10.2%)	–

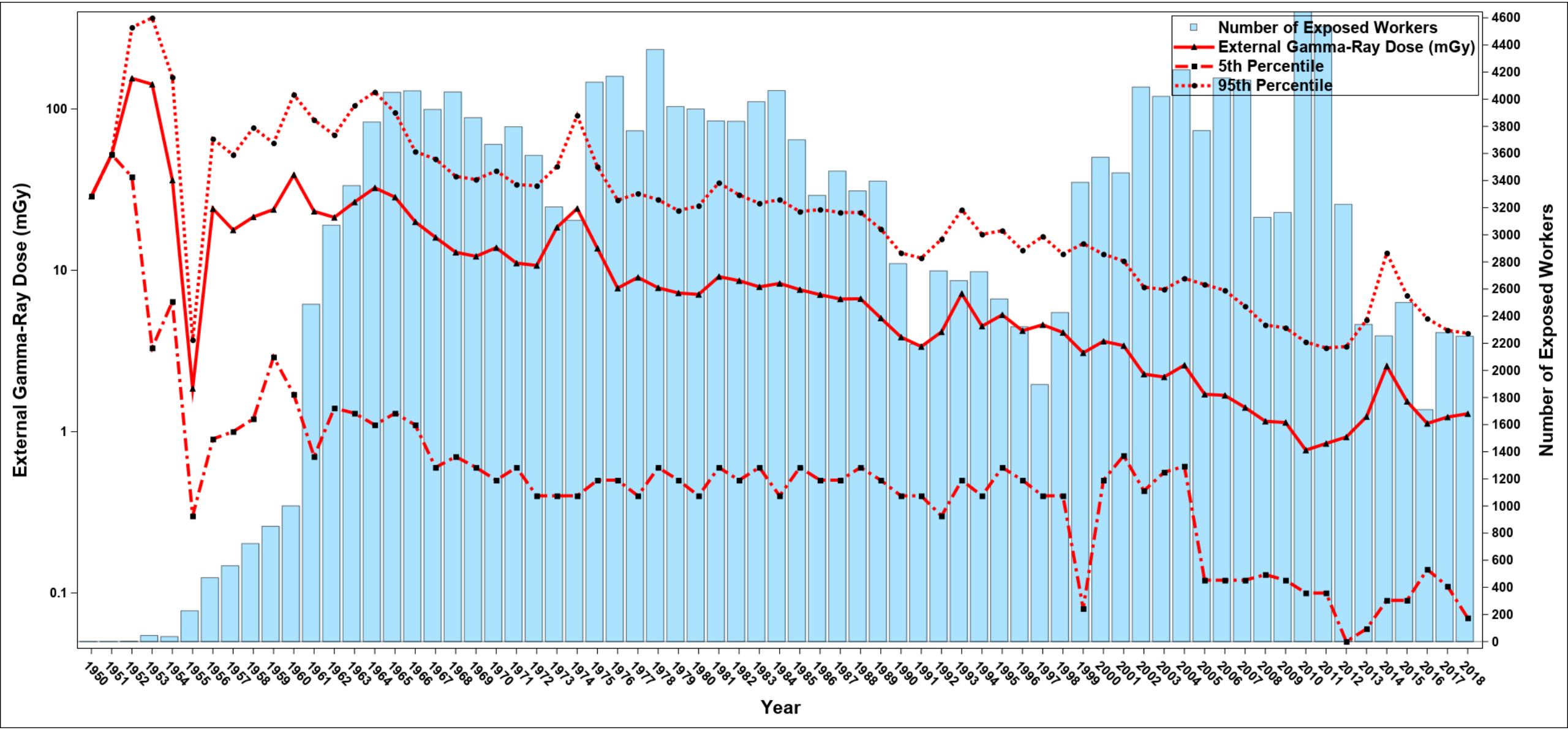
[a]Numbers represent workers who were monitored for internal or external exposures or both.
[b]Based on monitoring for internal exposure using both hospital and outpatient examinations.

Table 3. Descriptive characteristics of radiation exposures in the Seversk cohort (first employed 1950-2010, followed up 1950-2018).

Description	MEAN dose (range), mSv
Annual external whole-body gamma-ray doses from badge data (1950-2018)	
Full cohort (N=64,949)	26.93 (0-3,635.5)
Exposed (>0 mSv, n=21,324 (32.8%))	82.03
Monitoring for internal exposures from uranium using urine analyses (1953-2018)	
Exposed (at least one biomonitoring for internal exposures)	9,306 (14.3%)[a]

[a]Some workers have non-zero doses after the last day of employment (due to contractual work for SGCE)

Distribution of annual mean external Hp(10) dose from gamma-ray exposure (mGy) and number of workers, 1950-2018



Sex	Cumulative external dose from Hp(10) dose from gamma-ray exposure (mSv)							
	0	0-99	100-149	150-199	200-299	300-499	500-3,636	Total
Male	31,535	13,088	1,166	785	962	884	616	49,036
	64.3	26.7	2.4	1.6	2.0	1.8	1.3	
Female	12,090	3,453	173	91	77	25	4	15,913
	76.0	21.7	1.1	0.6	0.5	0.2	0.0	
Total	43,625	16,541	1,339	876	1,039	909	620	64,949
	67.2	25.5	2.1	1.4	1.6	1.4	1.0	100.0

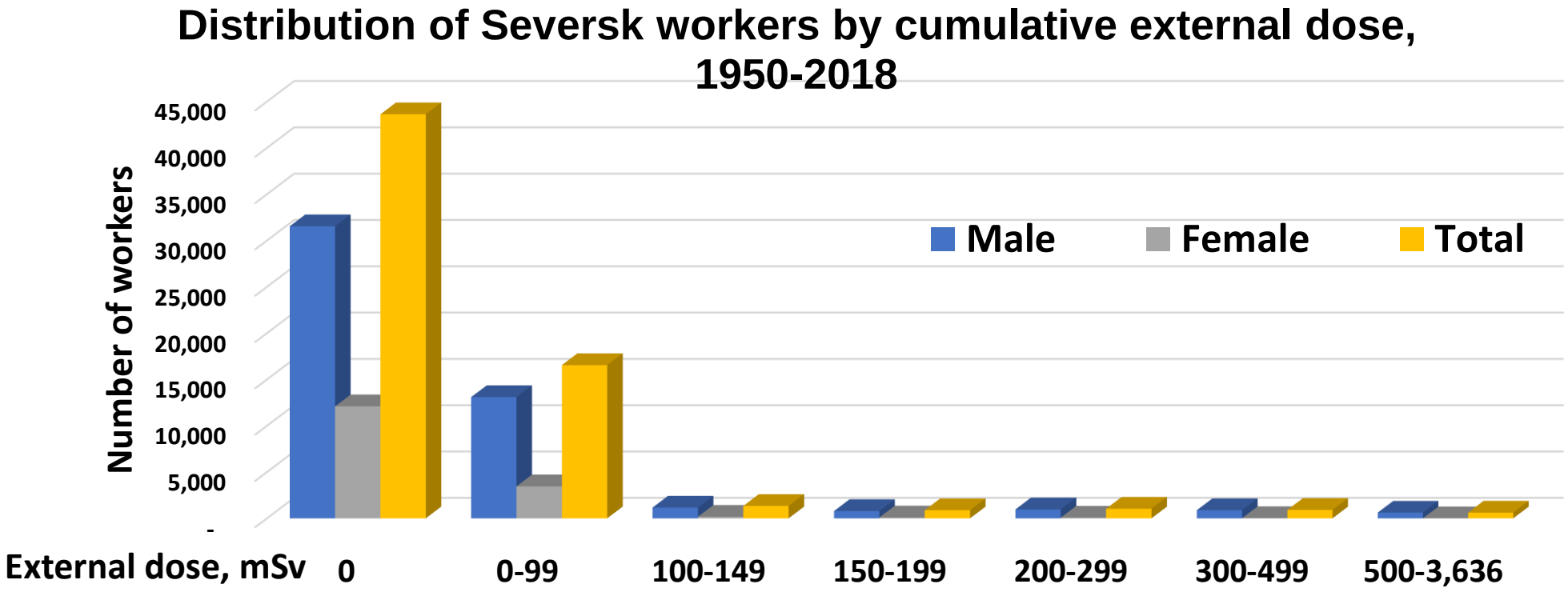


Table 4. MEDIAN cumulative external dose in the Seversk cohort, mSv.

Category	Value	N	Monitored							
			N	Total	Enrichment	Plutonium	Reactor	Radiochemical	Sublimation	Support Facility
Total		64,949	21,880	20.4	2.2	17.6	70.3	22.1	23.9	6.7
Sex	Male	49,036	17,959	24.4	2.4	21.5	81.9	23.7	28.4	6.5
	Female	15,913	3,921	9.3	1.5	5.5	25.4	15.5	10.7	6.9
Year first worked	1950-1959	12,871	3,104	72.2	1.8	45.3	142.7	46.5	102.0	21.0
	1960-1969	21,573	7,972	45.7	2.4	48.4	103.2	38.6	50.8	10.4
	1970-1979	12,064	4,005	15.5	1.6	23.2	45.9	16.0	13.2	9.0
	1980-1989	8,236	2,583	8.1	1.9	9.9	25.5	10.2	4.0	4.1
	1990-2010	10,205	4,216	4.2	2.5	4.6	10.1	7.4	4.2	2.7
Age first worked	14-19	23,652	8,649	23.4	2.4	19.9	71.4	25.8	29.6	6.4
	20-24	22,433	8,112	19.7	2.5	14.1	78.1	20.8	16.9	6.2
	25-29	9,419	2,924	20.4	1.5	19.0	67.2	21.4	26.5	7.1
	30-34	4,029	1,110	15.3	2.2	12.6	62.4	16.5	27.7	9.5
	35-74	5,416	1,085	11.7	0.7	22.0	23.7	14.7	14.3	6.7

Table 5. Outcomes in the Seversk cohort, N=64,949 (first employed 1950-2010, followed up 1950-2018).

Category	N (%)
MORTALITY follow-up, n (%)	
Died	17,680 (27.2)
Code of death known	16,171 (24.9)
Cancer code of death (ICD-10: C00.1-C97.9)	3,573 (5.5)
Cancer code of death excluding cancers of lung, liver and bone (ICD-10: C34, C22 and C40)	2,730 (4.2)
CVD deaths (ICD-10: I20-I25)	3,770 (5.8)
CANCER INCIDENCE follow-up, n (%)	
Cancer code (ICD-10: C00.1-C97.9)	6,204 (9.6)
Cancer code excluding cancers of lung, liver and bone (ICD-10: C34, C22 and C40)	5,267 (8.1)

Interim solid cancer incidence analysis (first employed 1950-2000, followed up 1950-2013, N=60,953)

- Created summary person-year tables for risk analyses using Epicure software.
- **Estimated radiation risks for solid cancer excluding cancers of the lung, liver and bone which are organs with primary plutonium deposition.**
- Estimated excess relative risks per sievert (ERR/Sv) of recorded external radiation dose and 95% confidence intervals (CIs) using Poisson regression.
- All models adjusted for categories of age, sex, calendar time, SGCE plant and smoking status by stratification.

Table 6. Estimates of relative risk by categories of cumulative external gamma-ray dose

Dose Category mSv	Mean Dose mSv	Cases No.	Cases %	Person-years No.	Person-years %	Relative Risk (RR)[a, b]	95% CI
0	0	2,838	71%	1,228,990	78%	1	
0.0001 - 199	37	936	23%	295,045	19%	1.02	0.95, 1.11
200 - 499	313	159	4%	40,140	3%	1.07	0.91, 1.26
500 - 999	664	61	1.5%	10,727	1%	1.50	1.16, 1.95
1,000 - 3,635	1,204	6	0.2%	1,347	0.09%	1.13	0.51, 2.54
ALL	119	4,000[c]	100%	1,576,250	100%		

[a] *$P_{heterogeneity}$ = 0.0657 (Degrees of Freedom = 4); $P_{linear\ trend}$ = 0.0113 (Degrees of Freedom = 1)*

[b] *Background rates adjusted for categories of age, sex, calendar time, SGChE plant and smoking status by stratification. Cumulative person-time weighted whole-body doses lagged by 5 years.*

[c] *Incident solid cancers other than lung, liver and bone.*

Table 7. Estimates of ERR/Sv by modifying factor, without adjustment for internal dose

Variable	Value	Cases	Person-years	Excess Relative Risk (ERR/Sv)[a, b]	95% CI
ALL CASES [P=0.04[c]]		4,000	1,576,250	0.34	0.012, 0.71
Sex [P=0.34[d]]	Male	2,525	1,137,290	0.25	-0.10, 0.66
	Female	1,475	438,961	0.67	-0.055, 1.57
Smoking status [P=0.02[d]]	Current smokers	797	285,305	0.64	0.20, 1.14
	Never smokers	3,203	1,290,940	-0.15	-0.55, 0.38
SGChE Plant [P=0.83[d]]	Reactor	424	157,754	0.25	<0, 2.16
	Radio-chemical	1,801	602,138	0.62	-0.034, 1.42
	Plutonium	593	284,405	0.08	-0.61, 1.07
	Enrichment	518	238,721	0.39	-0.16, 1.11
	Sublimation	380	180,598	0.45	-0.45, 1.79
	Support Facility	284	112,630	-0.17	<0, 0.88

[a] Background rates adjusted for categories of age, sex, calendar time, plant and smoking status by stratification. Cumulative person-time weighted whole-body doses lagged by 5 years. Incident solid cancers other than lung, liver and bone.

[b] Models additionally adjusted for variables investigated for possible interaction effects.

[c] P for significance of the dose term from the likelihood ratio test.

[d] P for interaction of the ERR/Sv across categories of the modifying factors of interest from the likelihood ratio test.

Table 7. Estimates of ERR/Sv by modifying factor, without adjustment for internal dose, *cont'ed*

Variable	Value	Cases	Person-years	Excess Relative Risk (ERR/Sv)[a, b]	95% CI
Attained age [P=0.22[d]]	<50 yrs	768	1,127,420	-0.28	<0, 0.68
	50-59 yrs	1,049	261,000	0.92	0.20, 1.83
	60-69 yrs	1,255	139,148	0.26	-0.23, 0.88
	70+ yrs	928	48,683	0.22	-0.35, 0.97
Age at start of employment [P=0.50[d]]	<20 yrs	137	246,374	0.67	-0.63, 1.97
	20-24 yrs	1,779	929,744	0.51	-0.014,1.03
	25-34 yrs	1,790	355,925	0.05	-0.53, 0.64
	35+ yrs	294	44,204	0.17	-1.33, 1.68

[a] Background rates adjusted for categories of age, sex, calendar time, plant and smoking status by stratification. Cumulative person-time weighted whole-body doses lagged by 5 years. Incident solid cancers other than lung, liver and bone.

[b] Models additionally adjusted for variables investigated for possible interaction effects.

[c] P for significance of the dose term from the likelihood ratio test.

[d] P for interaction of the ERR/Sv across categories of the modifying factors of interest from the likelihood ratio test.

Summary of results

- 4,000 incident solid cancers excluding cancers of the lung, liver and bone were recorded in the cohort during follow-up.
- A significant dose-response with cumulative gamma doses lagged by 5 years was identified, with smokers having significantly different risks from non-smokers (p=0.02)
- Entire cohort: ERR/Sv = 0.34, 95% CI: 0.012, 0.71
- Current smokers: ERR/Sv = 0.64, 95% CI: 0.20, 1.14
- Never smokers: ERR/Sv = -0.15, 95% CI: -0.55, 0.38
- Estimated radiation risks did not differ by sex, plant, attained age or age at start of employment (all p>0.2).

Conclusions

- This is the first dose-response analysis of incident solid cancers for workers employed at SGChE in Seversk, Russia.
- SGChE is one of the largest uranium processing complexes in the world and also one of the oldest.
- Radiation risks for non-smoking SGChE workers were comparable to risk estimates for nuclear reactor workers.
- Future analyses of SGChE workers should examine risks of external exposures with careful consideration of internal doses from various alpha-emitters.
- Extension of follow-up by 8 years increased the number of cases by 32%.

FUTURE DIRECTIONS

UCSF School of Medicine

(international Pooled Analysis of Uranium Workers)

UCSF

Study design

Inclusion criteria:

- Cohorts with workers involved in at least one of the uranium processing steps.
- Cohorts with individual exposure information for all workers.
  - Cohorts which satisfy the other criteria but have NO individual exposure information could be included in analyses for Aim 2 only.
- Cohorts with systematic follow-up.
- Cohorts with at least one publication (cohort profile ok).

Exclusion criteria:

- Exclude any workers who have been employed at any time during their career in the following:
  - underground or surface (pit) mines
  - nuclear reactors
  - storage of spent reactor fuel
  - reprocessing of ammunitions
  - radioactive waste management
  - industrial radiography
- Exclude workers ever employed in plutonium production (if known).
- Exclude workers with neutron doses or credible data about exposures to neutrons (if known).

Inclusion criteria

- Workers involved in any of the following stages of uranium processing cycle are eligible to participate in the study:
    1) Milling;
    2) Refining and Conversion;
    3) Enrichment;
    4) Reconversion and Fuel Fabrication

Descriptive characteristics of UPWs in iPAUW dose-response analyses

Descriptive Characteristics	iPAUW Total		
	Male	Female	Total
Number of UWs	35,000	874	35,874
Period of follow-up	1942-2020	1946-2020	1942-2020
Period of first hire	1932-2002	1942-2002	1932-2002
Person-years at risk	1,303,818	32,350	1,336,168
Mean years of follow-up	26-44	30-45	26-45
Mean year of birth	1921-1944	1926-1958	1921-1958
Mean year of hire	1951-1974	1965-1982	1951-1982
Mean age at hire	25-31	24-29	24-31
Mean years of employment	6-18	5-15	5-18
Vital status			
Alive	15,584	925	16,509
Dead*	17,327	838	18,165

*Cause of death known for 96-100%

Frequencies of selected outcomes in UPWs in iPAUW dose-response analyses

Disease Group[a]	iPAUW Total		
	Male	Female	Total*
All Causes of Death	11,947	498	17,303
All Malignant Neoplasms	3662	141	5,175
Cancer of Bronchus Trachea Lung	1101	38	1,548
Cancer of Bone	7	0	11
Cancer of Kidney	90	4	117
Cancer of Biliary Passages and Liver	96	4	124
Cancer of Large Intestine	200	14	322
Cancer of Central Nervous System	120	5	152
Non Hodgkins Lymphoma	126	3	166
Leukemia and Aleukemia	123	5	166
Multiple Myeloma	60	3	81
Nonmalignant Respiratory Disease	878	41	1,533
Nephritis and Nephrosis	114	13	152
Ischemic Heart Disease	2575	82	3,892
Cerebrovascular Disease	772	29	1,224
Dementia and Alzheimer's disease	234	28	427

*Includes causes of death from cohorts with currently unavailable distribution by sex

international Pooled Analysis of Uranium Workers (iPAUW)

Canada – L. Zablotska (UCSF), R. Lane (CNSC), D. Chambers and R. Stager (Arcadis Canada Inc.)

France – O. Laurent, E. Samson, D. Broggio, G. Drouet, F. Trompier (all IRSN), E. Davesne (CEA)

Germany – N. Fenske, V. Deffner, A. Giussani, V. Spielmann, M. Kreuzer (all BfS)

U.K. – R. Haylock, M. Gillies, A. Riddell, D. Gregoratto (all UK Health Security Agency)

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Seversk Pilot Study Collaborators

Seversk Biophisical Research Center (SBR Center):

- R.M. Takhauov
- I.V. Milto
- A.B. Karpov