Some Hazards of Using Exposure and Toxicological Data

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Overview

Exposure data and some characteristics

Toxicology data and some characteristics

Some data on cancer risks from early-life exposure

The risk assessment paradigm

HAZARD IDENTIFICATION

Can the agent cause cancer?

Is this relevant to humans?

Who may be more sensitive?

DOSE-RESPONSE ASSESSMENT

Estimate a dose-response curve

Account for high-to-low-dose, animal-to-human, route-to-route, and other differences

EXPOSURE ASSESSMENT

How do people come in contact with the agent?

How much are they exposed to?

RISK CHARACTERIZATION

Integrate *HAZARD*, *DOSE-RESPONSE*, and *EXPOSURE*

Describe the assessment's strengths, limitations, and research needs

How do people come in contact?

Important to consider all exposure pathways

- Food, drinking water, soil and dust, ambient air, . . .
- A safe level for exposure from food alone may not be safe when there is exposure through other pathways

Important to consider other chemicals with common mechanisms

Important to consider pesticidally inert ingredients that may be toxic chemicals in their own right

How much are people exposed to?

Generally, only aggregate exposure is estimated

- Average consumption of the full range of foods
- Average consumption across seasons
- Average consumption across lifetime

"Special diets"

- Still have same problem of aggregation over the subgroup

Focused on average pesticide residues

- Average level across country (percent of crop treated)

➔ *It may be useful to consider some maximal-exposure scenarios*

Studies used in carcinogen identification

Epidemiologic studies

Carcinogenicity bioassays

Mechanistic and other relevant data

- Absorption, distribution, metabolism, elimination
- Mechanisms of carcinogenesis
- Susceptibility data
- Toxicity at sites of tumor development, or at closely related sites
- Structure-activity information

Standard protocol for cancer bioassays

Experiments in male and female mice, male and female rats

High, medium, low dose groups; control group

High dose is set at a maximum tolerated dose

50 animals per group

Chemical administered in food or drinking water for 2 years

Cancer incidence is reported for each group of animals

Some characteristics of cancer bioassays

Exposure begins at 6-8 weeks, when rats and mice are mature

Chemical is administered with food, which may alter bioavailability or metabolism

Chemical is administered at a constant dose

Experiments are conducted one chemical at a time

- this may be an important consideration when people are exposed to multiple chemicals that act through similar mechanisms

Evaluating experimental animal data

Cancer in humans	Cancer in experimental animals — Preamble, Part B, Section 6(b)	Mechanistic and other relevant data

Sufficient evidence	Causal relationship has been established through either: - Multiple positive results (2+ species, studies, or sexes of GLP study) - Single unusual result (incidence, site/type, age at onset, or multi-site)
Limited evidence	Data suggest a carcinogenic effect but: (*e.g.*) from a single study, unresolved questions, benign tumours only, promoting activity only
Inadequate evidence	Studies permit no conclusion about a carcinogenic effect
Evidence suggesting lack of carcinogenicity	Adequate studies in at least two species show that the agent is not carcinogenic Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied

Children's cancer risks

"Children's risk" can mean different things to different people

- Effects manifest during childhood
- Early-life exposures that can contribute to effects at any time later in life

EPA (2005) has determined that cancer risks can be higher than those of adults for some early-life exposures

- 10x for 0-2 years
- 3x for 2-16 years

Some reasons why cancer risks can differ following early-life exposure

Differences in capacity to metabolize and clear chemicals

More frequent cell division during development

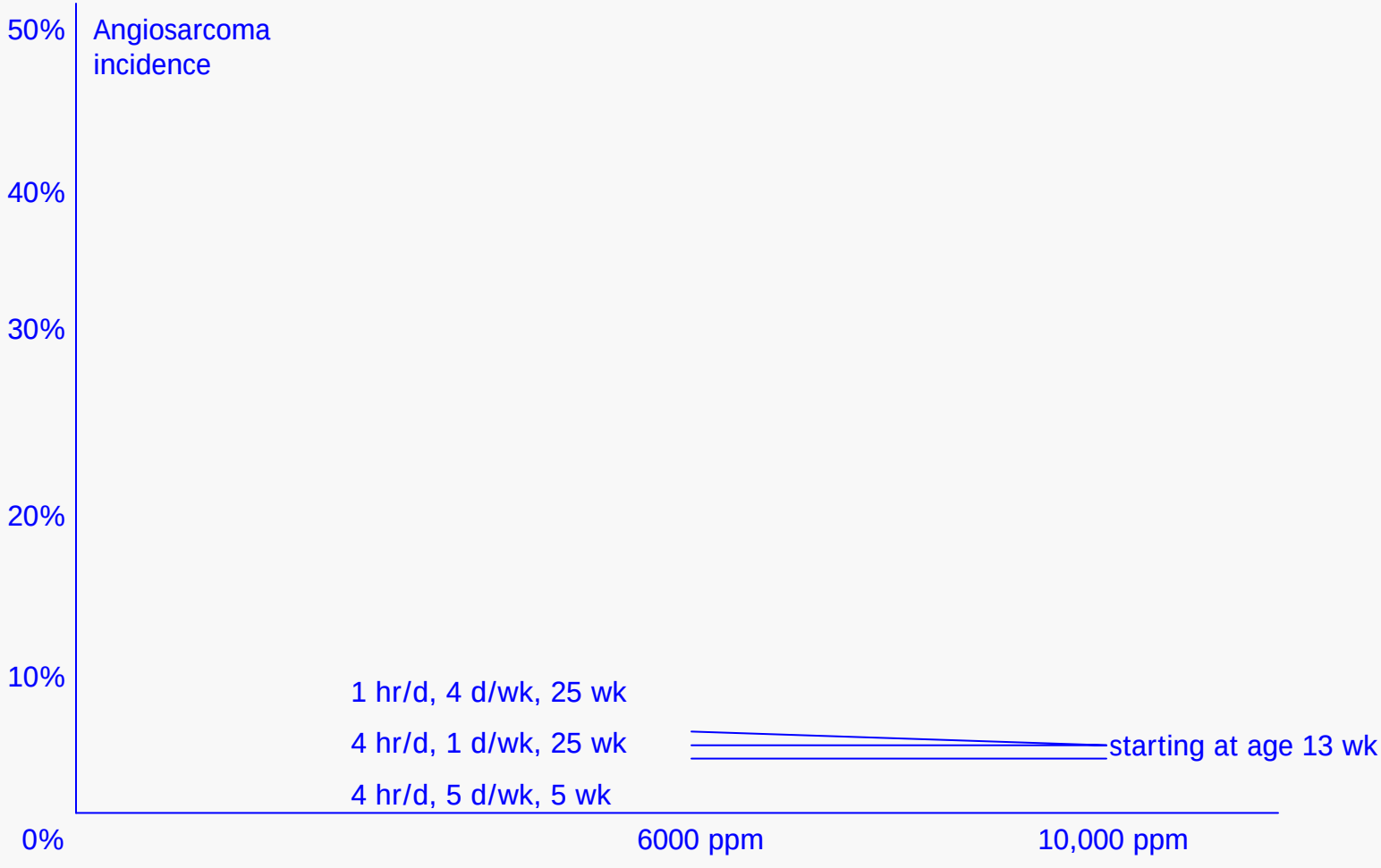
- Enhanced expression of mutations due to reduced time for repair of DNA lesions
- Clonal expansion of cells with unrepaired DNA damage

Immune system that is not fully functional

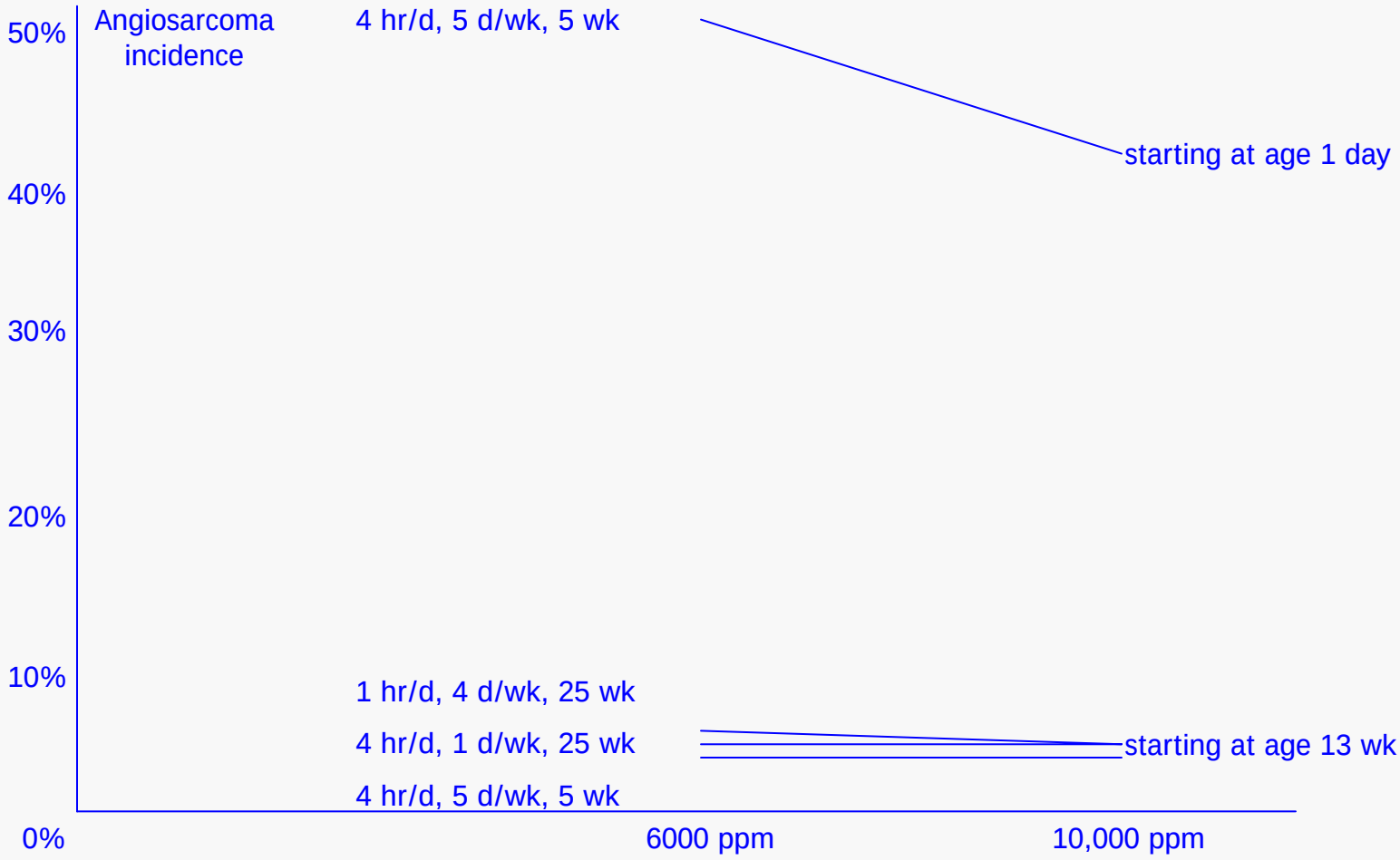
Hormonal systems that operate at different levels

Potential for developmental abnormalities to result in a predisposition to carcinogenic effects later in life

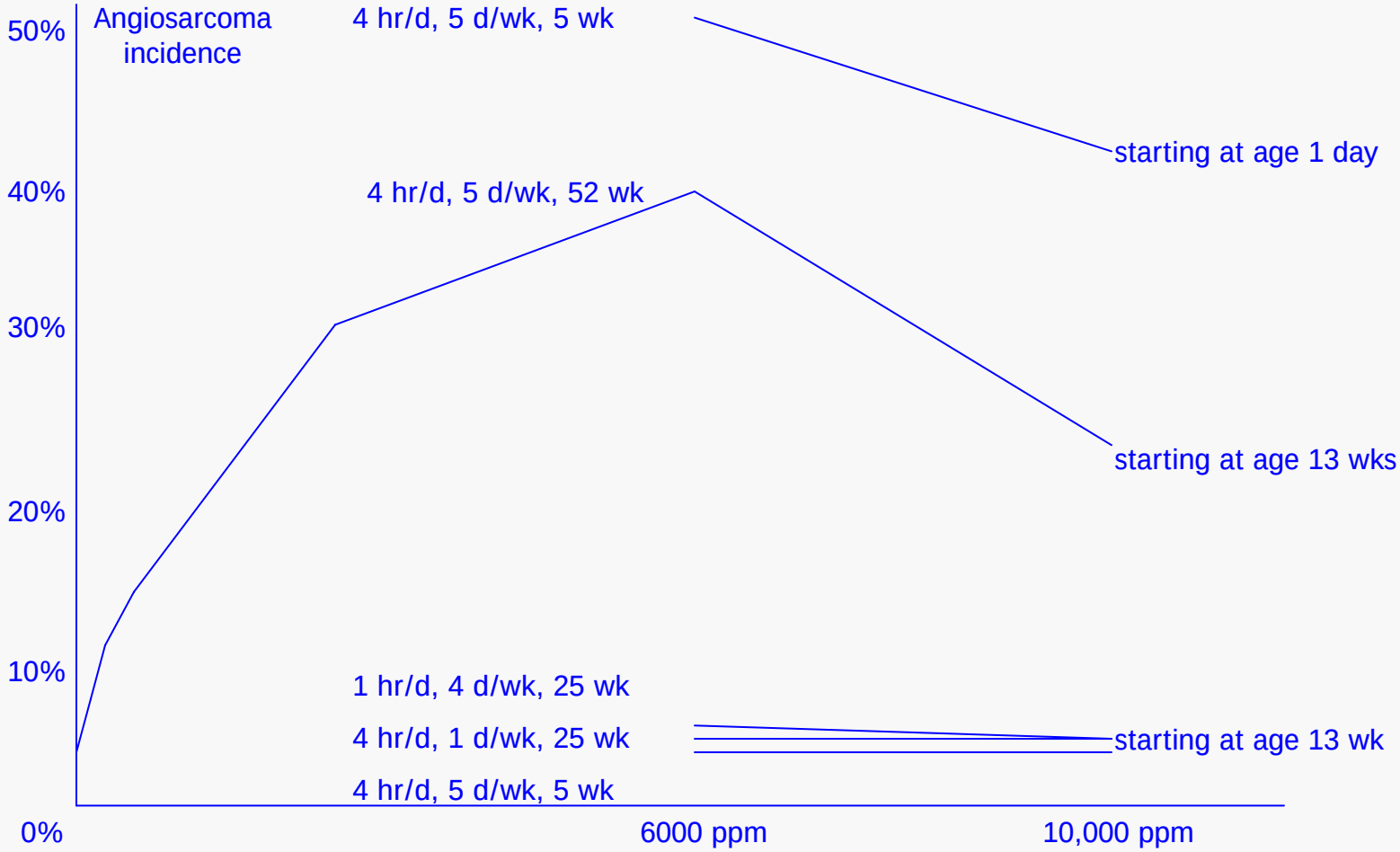
Vinyl chloride: hemangiosarcomas from short-term adult exposures



Vinyl chloride: hemangiosarcomas from short-term early-life exposure



Vinyl chloride: short-term early-life v. longer-term later-life exposure



Another example: DDT

Hepatocarcinogenesis in (C57BL/6J x C3HeB/FeJ)F_1 male mice		
	Tumor incidence	Increased incidence per week of dosing
Control	1/50 (2%)	
230 ug/d gavage, weeks 1-4	5/49 (10%)	2.0%
140 ppm diet, weeks 5-90	8/49 (16%)	0.14%
Both exposures	10/50 (20%)	0.2%
Source: Vesselinovitch et al (1979).		

Another example: dieldrin

Hepatocarcinogenesis in (C57BL/6J x C3HeB/FeJ)F_1 male mice		
	Tumor incidence	Increased incidence per week of dosing
Control	1/58 (2%)	
12.5 ug/d gavage, weeks 1-4	3/46 (7%)	1.25%
10 ppm diet, weeks 5-90	7/60 (12%)	0.12%
Both exposures	21/70 (30%)	0.31%
Source: Vesselinovitch et al (1979).		

A more complicated example: benzidine

Hepatocarcinogenesis in male and female mice		
	Tumor incidence in males	Tumor incidence in females
Control	1/98 (1%)	0/100 (0%)
Prenatal only	17/55 (31%)	2/62 (3%)
Preweaning only	62/65 (95%)	2/43 (5%)
Adult only	25/44 (59%)	48/50 (96%)
Prenatal + preweaning	49/49 (100%)	12/48 (25%)
Prenatal + preweaning + adult	50/50 (100%)	47/50 (94%)
Source: Vesselinovitch et al (1979)		

Another complicated example: safrole

Hepatocarcinogenesis in male and female mice		
	Tumor incidence in males	Tumor incidence in females
Control	1/98 (1%)	0/100 (0%)
Prenatal only	4/60 (7%)	0/65 (0%)
Preweaning only	27/83 (32%)	1/79 (1%)
Adult only	4/50 (8%)	28/50 (56%)
Prenatal + preweaning	25/67 (37%)	0/71 (0%)
Prenatal + preweaning + adult	25/50 (50%)	41/64 (64%)
Source: Vesselinovitch et al (1979)		

A case of multiple risk windows: DMBA

Tumor responses in Wistar rats following a single gavage dose			
	Fibrosarcoma in males	Fibrosarcoma in females	Mammary carcinomas
Before week 2	11/23 (48%)	11/50 (22%)	4/50 (8%)
During weeks 5-8	0/23 (0%)	0/25 (0%)	14/25 (56%)
During week 26	0/34 (0%)	0/26 (0%)	4/26 (15%)
Source: Meranze et al (1969) Mammary carcinoma window replicated in Sprague-Dawley rats by Russo et al (1979)			

A case where cancer risk depends on age at first exposure: DEN

Relative risk of tumors in Colworth rats following "lifetime" exposure to DEN in drinking water, relative to starting at age 6 weeks		
	Relative risk of liver tumors	Relative risk of esophageal tumors
Dosing begins at age 3 weeks	2.9 x	1.2 x
Dosing begins at age 6 weeks (baseline experiment)	- 1 -	- 1 -
Dosing begins at age 20 weeks	0.5 x	0.9 x
Source: Peto et al (1984)		

Early-life sensitivity may hold the key to a puzzling old bioassay

Gastric tumors in mice fed benzo[*a*]pyrene		
Dose (ppm diet)	Tumor incidence	
0	0/289 (0%)	
1	0/25 (0%)	
10	0/24 (0%)	
20	1/23 (5%)	
30	0/37 (0%)	
40	1/40 (2%)	
45	4/40 (10%)	
50	24/34 (70%)	
100	19/23 (82%)	
250	66/73 (90%)	
Source: Neal and Rigdon (1967)		

Early-life sensitivity may hold the key to a puzzling old bioassay

Gastric tumors in mice fed benzo[*a*]pyrene		
Dose (ppm diet)	Tumor incidence	Age at first dose (days)
0	0/289 (0%)	
1	0/25 (0%)	30
10	0/24 (0%)	30
20	1/23 (5%)	116
30	0/37 (0%)	33 or 67
40	1/40 (2%)	33 or 101
45	4/40 (10%)	31 or 71
50	24/34 (70%)	17 or 22
100	19/23 (82%)	20 or 24
250	66/73 (90%)	18 or 20
Source: Neal and Rigdon (1967)		

Numerous injection studies show similar results

Benzo[*a*]pyrene: liver tumors, lung tumors

DEN: liver tumors, but decreased sensitivity to lung tumors

DMBA: lung tumors, lymphomas, mammary carcinomas

ENU: Liver tumors, nerve tissue tumors

3-MC: Lung tumors

Urethane: Liver tumors, lung tumors, leukaemia

X rays: liver tumors

Evidence that effects from perinatal and adult exposures can differ

Vinyl chloride: Hepatomas occurred in rats only following early post-natal exposure

DPH: Perinatal+adult exposure increased liver tumors in male mice (but not in females or in rats)

ETU: Perinatal+adult exposure increased thyroid tumors in rats (but not in mice)

PBBs: Perinatal+adult exposure increased liver tumors in rats and mice

Saccharin: Bladder tumors occurred only in the male offspring of female rats fed saccharin

Susceptibility induced by perinatal exposure to estrogenic chemicals

DES

- Vaginal, cervical adenocarcinomas in young women exposed *in utero*
- There is also limited evidence for endometrial cancer and testicular cancer from exposure *in utero*

Genistein: Prenatal exposure increases later susceptibility to DMBA-induced mammary tumors

Tamoxifen: Prenatal exposure increases later susceptibility to DMBA-induced mammary tumors

Other studies in progress

Summary

With exposure data, it is important to remember that reasonable individual exposure scenarios may exceed the estimates of “high-end” exposure

With toxicological data it is important to remember that risk estimates are derived for the “average” response and that there are individuals of higher and lower susceptibility

Exposure during early life-stages are generally not studied in so-called “lifetime” bioassays

What is the risk for individuals with high exposure and high susceptibility?

Radiation risk coefficients are often higher for childhood exposure

	M 0-9y	M 20-29y	M 40+y	F 0-9y	F 20-29y	F 40+y
Residual	0.5349	0.6093 (.9x)	0.0407 (13x)	1.122	0.885 (1.3x)	0.1175 (10x)
Colon	2.290	0.2787 (8x)	0.0888 (26x)	3.265	0.6183 (5x)	0.1921 (17x)
Lung	0.4480	0.0435 (10x)	0.1680 (3x)	1.359	0.1620 (8x)	0.6047 (2x)
Breast				0.7000	0.3000 (2x)	0.1000 (7x)
Leukemia	982.3	416.6 (2x)	143.6 (7x)	1176	370.0 (3x)	157.1 (7x)
Bladder	1.037	1.037 (1x)	1.037 (1x)	1.049	1.049 (1x)	1.049 (1x)
Stomach	1.223	2.044 (.6x)	0.2745 (4x)	3.581	4.552 (.8x)	0.5424 (7x)
Thyroid	0.1667	0.08333 (2x)	0.08333 (2x)	0.3333	0.1667 (2x)	0.1667 (2x)
Ovary				0.7185	0.7185 (1x)	0.7185 (1x)
Liver	0.9877	0.9877 (1x)	0.9877 (1x)	0.9877	0.9877 (1x)	0.9877 (1x)
Esophagus	0.2877	0.2877 (1x)	0.2877 (1x)	1.805	1.805 (1x)	1.805 (1x)
Kidney	0.2938	0.2938 (1x)	0.2938 (1x)	0.2938	0.2938 (1x)	0.2938 (1x)
Bone	0.09387	0.09387 (1x)	0.09387 (1x)	0.09387	0.09387 (1x)	0.09387 (1x)
Skin	0.06597	0.06597 (1x)	0.06597 (1x)	0.06597	0.06597 (1x)	0.06597 (1x)

Source: EPA (1999) Cancer risk coefficients for environmental exposure to radionuclides