TR 7/2010

Technical report:

# HENVINET

## Evaluation questionnaire – Causal chain for cancer

Aileen Yang[1)] and Alena Bartonova[1)], Editors

**Authors:**
Aleksandra Fucic[2)] and Domenico Franco Merlo[3)]

[1)] Norwegian Institute for Air Research, Kjeller, Norway
[2)] Institute for Medical Research and Occupational Health, Zagreb, Croatia
[3)] National Cancer Research Institute, Epidemiology and Biostatistics & Clinical Trials and Bioethics, Genoa, Italy

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HEALTH AND ENVIRONMENT NETWORK

# Evaluation questionnaire – Causal Chain for cancer

## Prelude

Thank you very much for participating in this expert evaluation, conducted in the context of the HENVINET project. Before beginning, we would ask you to provide some basic information about yourself.

Name:_____

E- mail address:_____

Institutional affiliation:_____

5 keywords describing your area of expertise:

1. _____ 2. _____ 3._____ 4._____ 5. _____

# Introduction

In the HENVINET project we focus on four types of diseases, including “cancer”, and its association with environmental exposures. This is an evaluation of the quality of the scientific knowledge of various aspects of the cause-effect relationship between our living environment and increased risk of cancer development. Occupational exposure to carcinogens is not included.

The goal is to identify knowledge gaps and potential agreement or disagreement on this between you and your expert colleagues in the field. Ultimately, the aim is to discuss the implications of the results of the evaluation for policy and research.

There are six cancer types currently available for review, and each can be considered separately. Some are more complex than others and will therefore take longer to answer.

Sometimes experts feel uncomfortable performing evaluations on the basis of their scientific intuition and experience. We ask for your considered opinion based on the quality of your scientific work and rely on the fact that your broad experience in the field will suffice to help achieve a qualified understanding of the issues under discussion here.

Your own expert judgment will be complimented by those of at least 10 of your colleagues in the field, as well as by a thorough review of the literature on this issue. All this information will be considered by a panel of experts during a workshop at a later time, on the impact of environment factors on health. On this basis, the experts will provide recommendations to policy makers with regards to research and problem solving strategies.

We hope that this will address any concerns you may have. If not, please contact Aleksandra Fucic: Aleksandra Fucic ( afucic@imi.hr) or Franco Merlo (franco.merlo@istge.it).

We appreciate your participation very much and, on behalf of the HENVINET consortium, we thank you for your time.

## Current state of the art

Before evaluating the diagrams, please take your take you time to read the general considerations summarised on the next page, which gives an overview of the environment-cancer issue and - most important - the methodology that has been followed in constructing the diagrams (the best scientific evidence available and the strength of association).

**Cancer accounted for more than 7 million deaths worldwide in 2000, and 10 million new cancer cases were diagnosed. More than 60% of cancer deaths occurred in the developing regions. Lung cancer was the most common, followed by cancers of the stomach, liver, colon and rectum, and breast. Cancer in all ages is a result of the interaction between age, genetic and environmental factors. Differences in lifestyle and environmental exposures have been assumed to be a major reason for the various geographical distribution of cancer. Genetic factors and ethnic variations account for some part of regional differences (EEA report 10/2005).**

Environmental factors are important in the pathogenesis of cancer, but if lifestyle-related environmental factors are excluded, the only environmental factor for which there is a proven connection to cancer development is ionising radiation. The carcinogenic effect of it arises through direct damage to DNA. The connection between non-ionising radiation and skin cancer is also well established: Approximately 80-90% of all skin cancers can be related to UV radiation.

There is a scientific debate that long-term, low-dose exposure to both low and high frequency electromagnetic fields can cause adverse health effects. Indeed recent systematic reviews showed a statistical association between low and high frequency electromagnetic fields and childhood leukaemia and brain tumors. However, the mechanisms by which these weak fields could cause leukaemia or brain tumors remain unclear and the evidence is not conclusive.

Some chemicals clearly cause cancers in some exposed groups, but the role of chemicals in overall cancer causation is unclear and disputed. Any excess cancer mortality from a chemical pollutant is likely to be restricted to a section of the population, so mortality rates for entire populations can often be weak and insensitive indicators of environmental health effects from pollution. Moreover, people are exposed indoor and outdoor to complex mixtures present in air, water, and food. Air pollution, for example, includes carcinogenic chemicals such as benzene and polycyclic aromatic hydrocarbons (PAH). Fried and smoked food items may contain carcinogenic substances as well.

Several studies showed a positive association between local traffic density and childhood leukaemia. Only a limited number of studies have evaluated the potential risk of living nearby hazardous industrial sites, which may also be a source of carcinogenic chemicals.

Cancer in European children younger than 15 years is in general terms rare, but is still one of the most common causes of death in children in industrialised countries. The most common childhood cancers are leukaemia and brain tumours. A small but significant increase in childhood cancers has been noted since the mid- 1980s, which could have been explained by better diagnostic methods, but an additional component from environmental exposures cannot be excluded.

Children are particularly at risk from chemicals because of their greater biological sensitivity and greater exposure to environmental pollution relative to body weight. Although no specific parental occupational exposure was definitely established as a cause of childhood cancer, several occupations have been found to

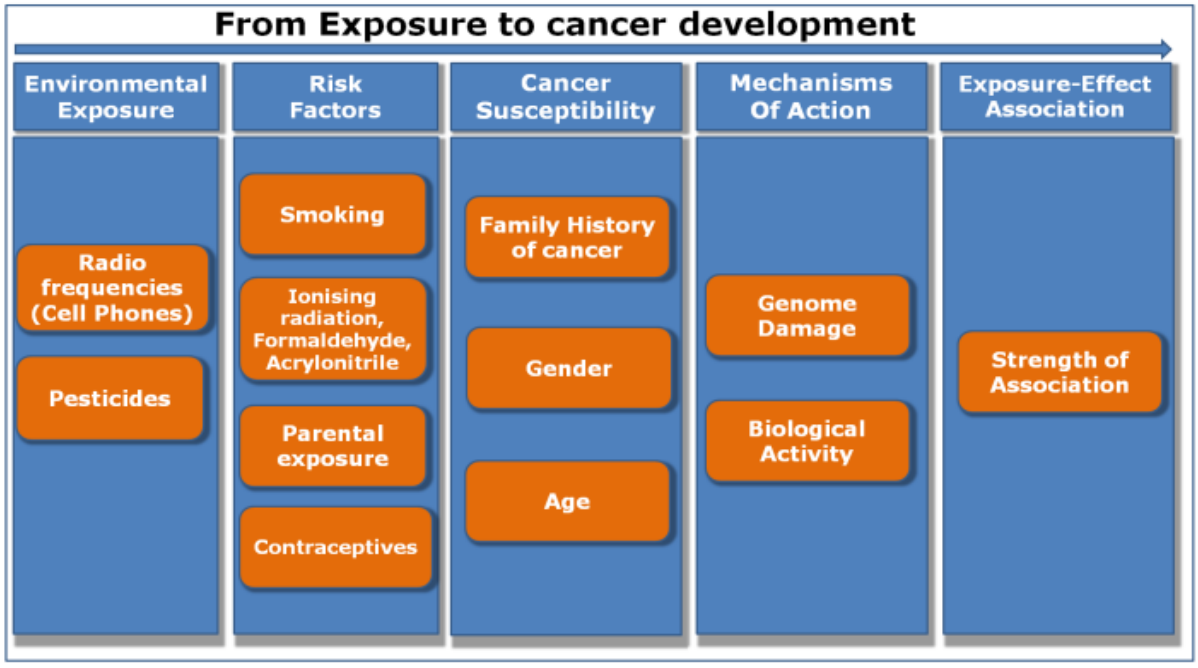
be statistically associated with it: increased risk of brain cancer has been related to maternal exposure to high levels of solvents; occurrence of brain tumours has been related to paternal exposure to pesticides and PAH.

Many studies suggest that most cancers in children are initiated before birth. Greater susceptibility of the foetus and young child has physiological reasons since they are undergoing multiple processes of growth and differentiation and the potential for mutations to arise following transplacental exposure to a carcinogen is therefore much greater in the growing foetus and child. Chemical pollutants which are carcinogens and that may affect reproductive health and newborn children include certain metals (e.g. lead and methyl mercury), pesticides (e.g. DDT), and industrial chemicals (e.g. PCBs). .
Exposure to exogenous carcinogens in childhood may have an important effect on cancer risk in adult life.
Recent epidemiological studies have demonstrated the important role of genetic susceptibility in cancer development. Individual susceptibility to cancer may result from several host factors including differences in metabolism, DNA repair, altered expression of protooncogenes and tumour suppressor genes. Since most carcinogens require metabolic activation before binding to DNA, individual features of carcinogen metabolism may facilitate or help to block the development of environmental cancer.


Figure 1: Hierachy of different research designs, ranked from weakest to strongest.

The evidence of the exposure-effect association (causal association) in human studies comes from different study designs. Some designs are considered to provide a stronger level of evidence than others. Based on their inherent characteristics their hierarchy is graphically summarized in a pyramid. The pyramid depicts the strength of the evidence for commonly used research designs (from the weakest to the strongest). Such hierarchy should be taken into account in evaluating the published evidence.

## Brain cancer

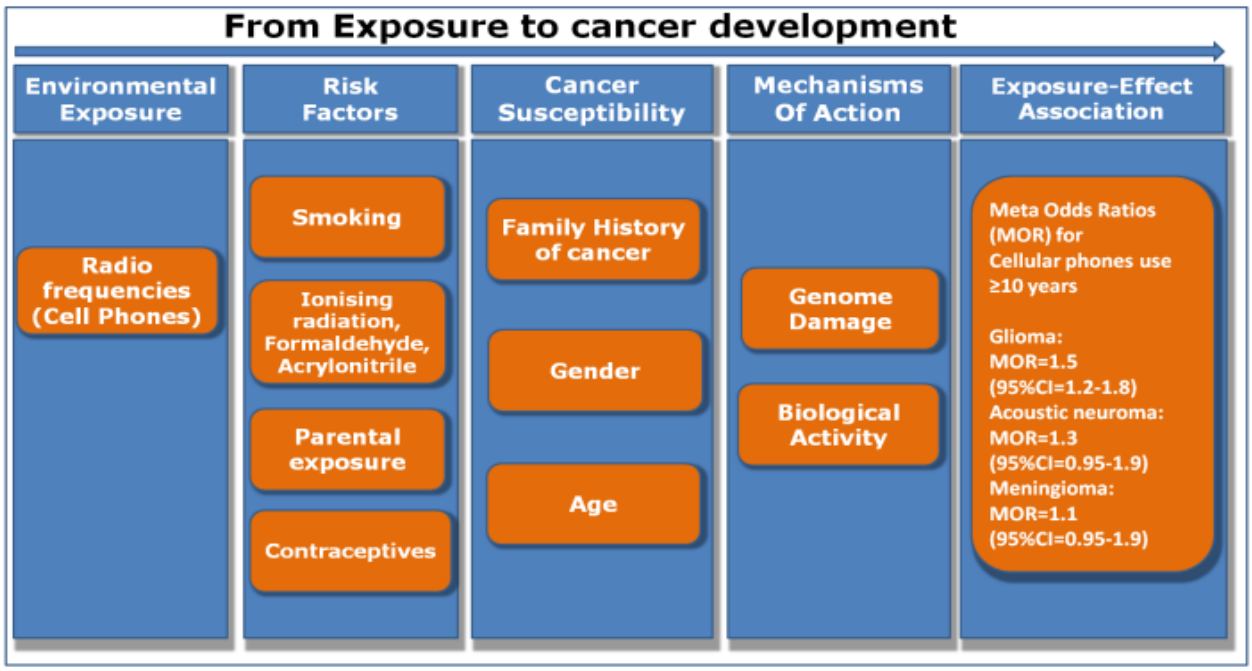



There are more than 120 types of brain tumors. Today, most medical institutions use the World Health Organization (WHO) classification system to identify brain tumors (WHO Classification of Tumors of the CNS, 2007). The WHO classifies brain tumors by cell origin and how the cells behave.

| | |
|---|---|
| Tumors of neuroepithelial tissue<br>(astrocytic tumors)<br>(oligodendroglial tumors)<br>(oligoastrocytic tumors)<br>(ependymal tumors)<br>(choroid plexus tumors)<br>(other neuroepithelial tumors)<br>(neuronal and mixed neuronal – glial tumors)<br>(tumors of the pineal region)<br>(embryonal tumors)*Tumors of cranial and paraspinal nerves*<br>(other neoplasms related to the meninges) | Tumors of the meninges<br>(tumors of meningothelial cells)<br>(mesenchymal tumors)<br>(primary melanocytic lesions)<br>*Lymphomas and hematopoietic neoplasms*<br>*Germ cell tumors*<br>*Tumors of the sellar region*<br>*Metastatic tumor* |

It is important important to note benign brain tumors located in a vital area can be considered life–threatening and just as difficult to treat as malignant brain tumors.

## Brain tumors – Radiofrequencies




**RISK FACTORS**

*SMOKING*

Cigarette smoke contains formaldehyde a chemical know to cause brain tumors.

*IONISING RADIATION, FORMALDEHYDE, ACRYLONITRILE.*

Increased risk of brain tumor has been reported in occupationally exposed workers.

*PARENTAL EXPOSURE*

Parental exposure to solvents has been associated with brain tumors in children.

*CONTRACEPTIVES*

Increased risk in women who used long-acting hormonal contraceptives (>= 10 years): OR= 2.7 (95%CI, 0.9-7.5).

**CANCER SUSCEPTIBILITY**

*FAMILY HISTORY OF CANCER*

There is evidence that subjects with family members who have gliomas (a specific type of brain cancer) may have a high risk to develop glioma.

*GENDER*

Brain tumors occur more frequently in males than in females.
Meningiomas are more common in females than in males.

*AGE*

Radiofrequencies exposure (SAR, i.e., specific absorption rate ) of peripheral brain sub-regions are two times higher in children than in adults: skin and bone layers in children are thinner in children.
Brain tumors are the second most common cancer in children and are more common in children aged <8 years.

**MECHANISMS OF ACTION**

*GENOME DAMAGE*
Radiofrequency radiation may enhance chemically induced reactive oxygen species production and DNA damage. Radiofrequency in vitro causes increased levels of aneuploidy.

*BIOLOGICAL ACTIVITY*
Radiofrequency causes production of free radicals

## Questions

**What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to radiofrequency from using cell phones and the risk of brain tumours?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
|---|---|---|---|---|
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**What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to radiofrequency and cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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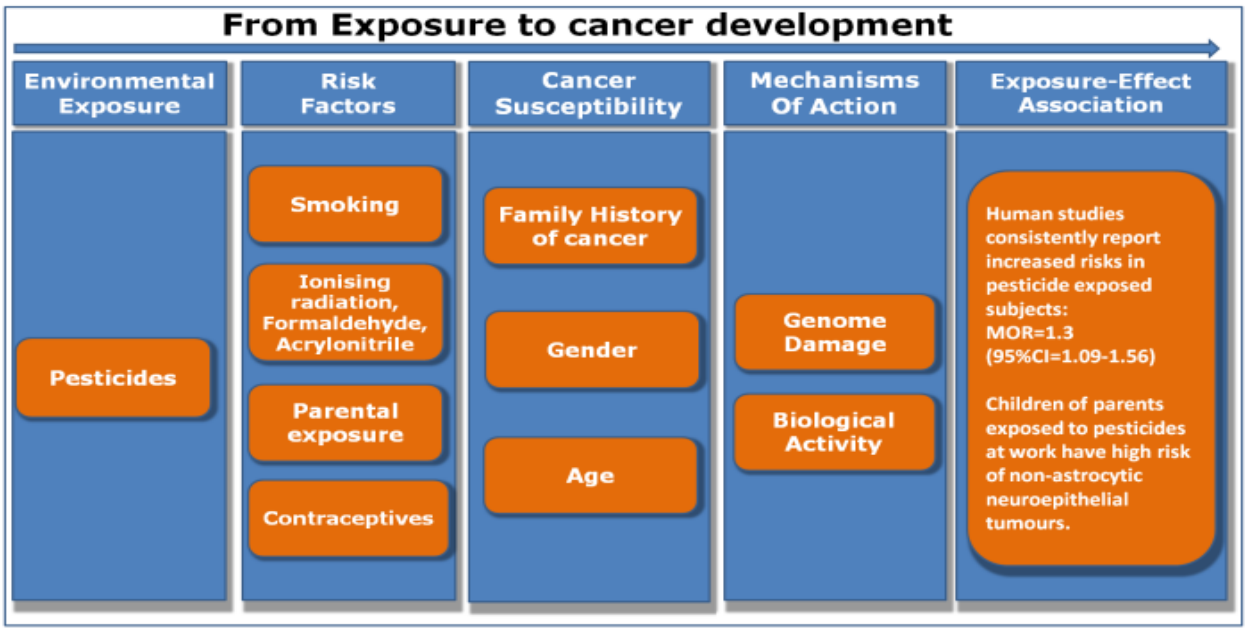
**Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle)?**

In favor ☐ Against ☐

**If you have any specific policy actions in mind, please specify them here:**

## Brain Cancer – Pesticides




**RISK FACTORS**

*SMOKING*

Cigarette smoke contains formaldehyde a chemical know to cause brain tumors.

*IONISING RADIATION, FORMALDEHYDE, ACRYLONITRILE*

Increased risk of brain tumor have been reported in occupationally exposed subjects.

*CONTRACEPTIVES*

Increased risk in women who used long-acting hormonal contraceptives (>= 10 years): OR= 2.7 (95%CI, 0.9-7.5).

*PARENTAL EXPOSURE*

Parental exposure to solvents has been associated with brain tumors in children.

**CANCER SUSCEPTIBILITY**

*GENDER*

Brain tumors occur more frequently in males than in females.

Meningiomas are more common in females than in males.

*FAMILY HISTORY*

There is evidence that subject with family members who have gliomas (a specific type of brain cancer) may have a high risk to develop glioma.

*AGE*

Children may be sensitive to the carcinogenic exposure to pesticides: increased risks in children are greater than in adults.

Brain tumors are the second most common cancer in children and are more common in children aged <8 years.

**MECHANISMS OF ACTION**

*GENOME DAMAGE*
Chromosome aberrations and increased frequency of micronuclei have been detected in the majority of studies, mitotic arrest, clastogens, aneugens, some pesticides cause disturbances of mitotic spindle.

*BIOLOGICAL ACTIVITY*
Translocations or clonotypic gene fusion sequences match that of later leukemic blasts in blood spots (Guthrie card), some pesticides are xenoestrogens, ROS production.

## Questions

**What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to pesticides and the risk of brain tumours?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to radiofrequency and brain cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce pesticide exposure?**

In favor ☐ Against ☐

**If you have any specific policy actions in mind, please specify them here:**

| |
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| |

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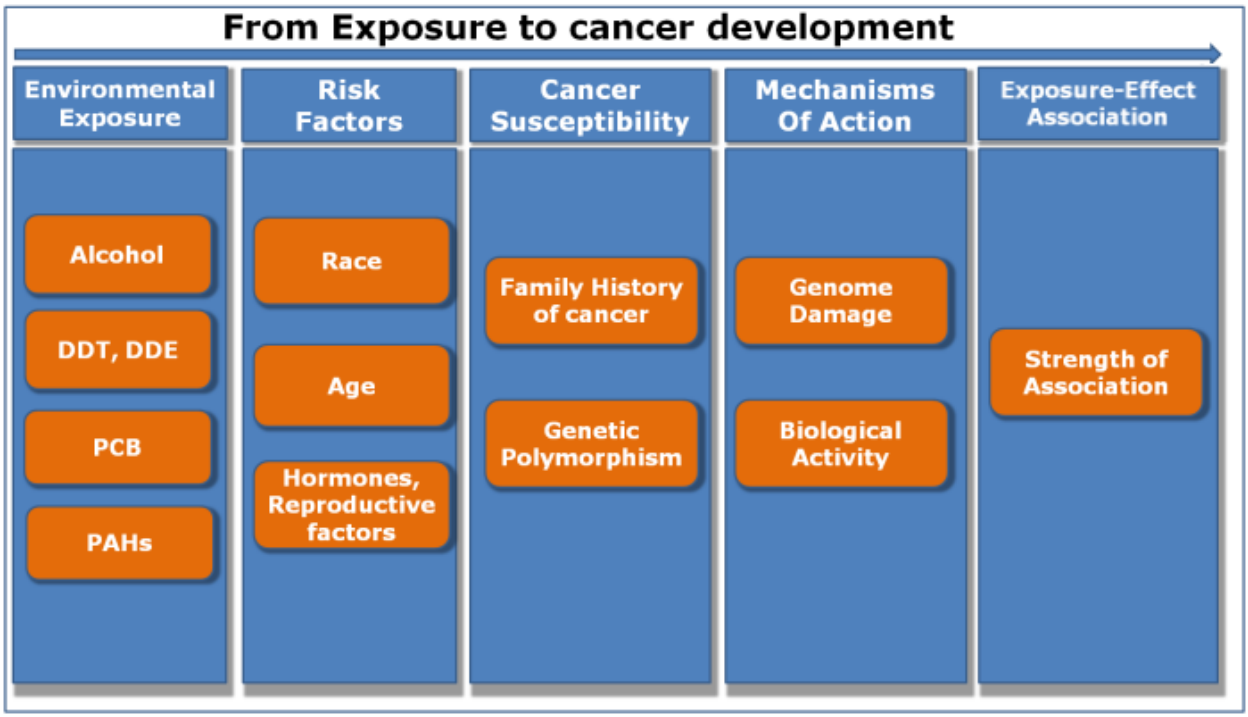
## Breast Tumors

**Benign epithelial lesions** with no significant tendency to malignant transformation include:

- Adenoma:
    - Ductal
    - Lactating
    - Tubular
- Adenosis:
    - apocrine
    - Blunt duct
    - Microglandular
    - Sclerosing
- Fibroadenoma
- Radial scar/complex sclerosing lesions

**Invasive breast carcinomas** are divided into two major categories on the basis of their cytoarchitectural features:

- ***Invasive ductal carcinoma:***
    - Acinic cell carcinoma
    - Adenoid cystic carcinoma
    - Apocrine carcinoma
    - Cribriform carcinoma
    - Glycogen-rich/clear cell
    - inflammatory carcinoma
    - lipid-rich carcinoma
    - medullary carcinoma
    - metaplastic carcinoma
    - micropapillary carcinoma
    - mucinous carcinoma
    - neuroendocrine carcinoma
    - oncocytic carcinoma
    - papillary carcinoma
    - sebaceous carcinoma
    - tubular carcinoma
- ***Invasive lobular carcinoma:***
    - pleomorphic
    - signet ring cell




**RISK FACTORS (are valid for ALL exposures).**

*RACE*

Breast cancer risk is higher in white women than African American, Latina or Asian women.

*AGE*

Breast cancer risk increase with age and most cases of breast cancer occur in women over 60.
Increased risk in premenopausal women lacking for the GSTM1 and GSTT1 genes.

*HORMONES*

Estrogens and other hormones, including pharmaceutical hormones, and lack of exercise could affect hormone levels and reproductive characteristics, which are associated with breast cancer development.

**CANCER SUSCEPTIBILITY (are valid for ALL exposures)**

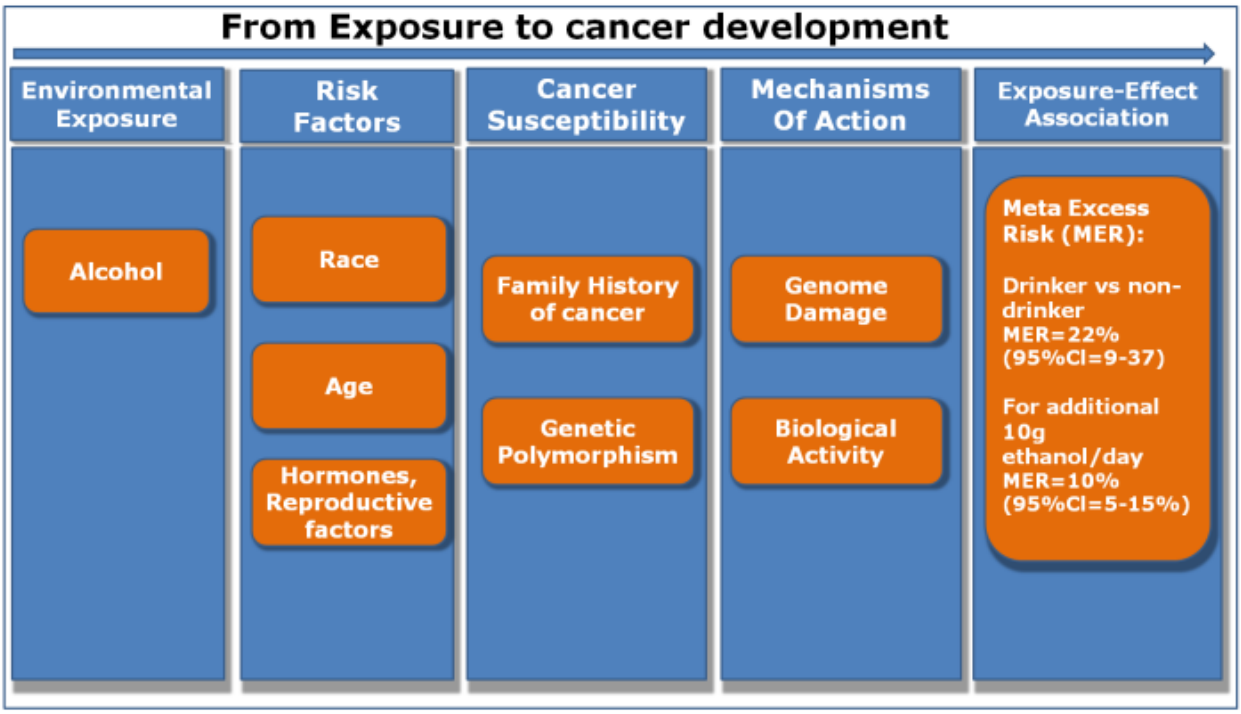
*FAMILY HISTORY OF CANCER*

Breast cancer risk is higher if a woman first degree relative (mother, sister, daughter) had breast cancer and if a member of her family got breast cancer before age 40.
BRCA1-mutation carriers by age 70 years have a cumulative risks MCR=65% (95%CI=44%-78%) ; BRCA2-mutation carriers by age 70 years: MCR=45% (95%CI=31%-56%).

*GENETIC POLYMORPHYSMS*

Effect of XRCC1 polymorphisms Arg280His variant in Asian population MOR=2.27 (95%CI=0.82-6.31) and Arg399Gln variant in Asian population MOR=1.59 (95%CI=1.22-2.09).

## Breast tumors - Alcohol




**MECHANISMS OF ACTION**

*GENOME DAMAGE*

Alcohol increases frequency of chromosome aberrations, sister chromatid exchange frequency, micronucleus frequency, chromosome damage in oncogenic regions.

*BIOLOGICAL ACTIVITY*

Alcohol increases estrogen levels, clastogen, aneugen, ROS production, interfers with DNA methylation.

### Question

**What is your level of confidence in the current scientists' ability to predict the impact of exposure to alcohol and the risk of breast cancer?**

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
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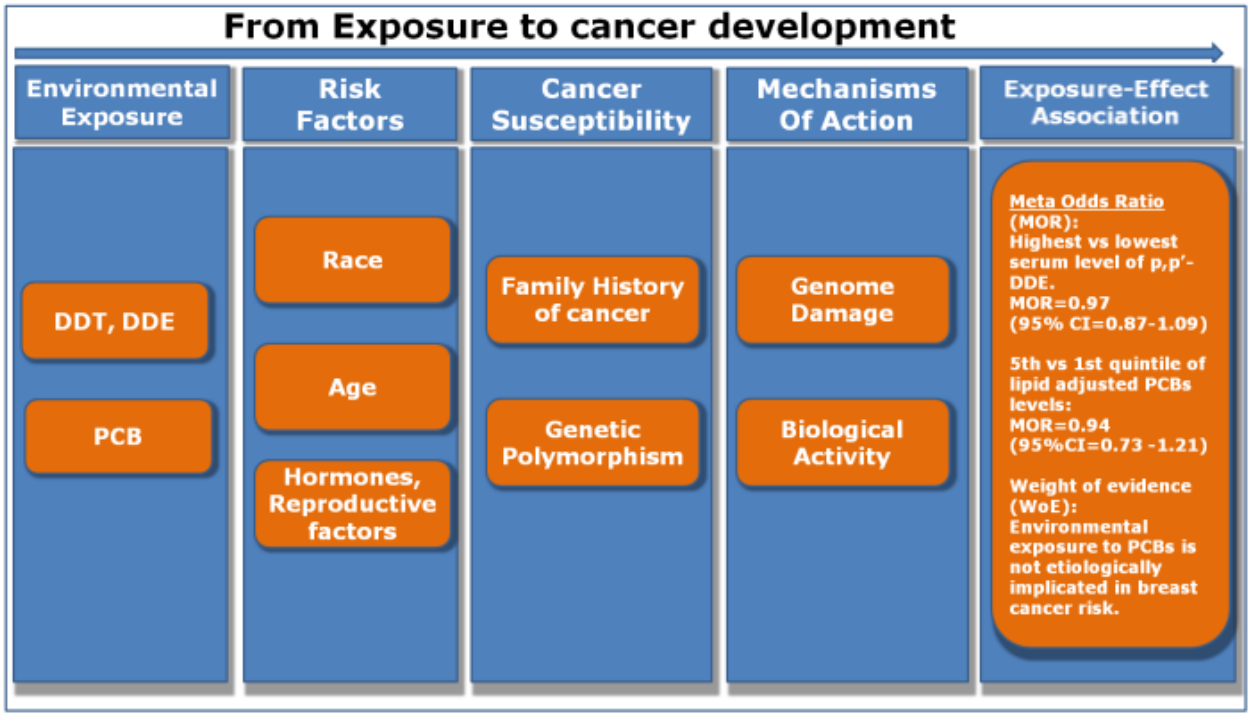
## Breast tumors – DDE, DDT, PCB




**MECHANISMS OF ACTION**

*GENOME DAMAGE*

Organochlorine insecticides DDT,DDE and PCB increased frequency of chromosome aberrations, sister chromatid exchange frequency, micronucleus frequency, chromosome damage in oncogenic regions.

*BIOLOGICAL ACTIVITY*

Organochlorine insecticides DDT,DDE and PCB increases estrogen levels, clastogen, aneugen, ROS production, interfers with DNA methylation.

Animal studies shows increased susceptibility to induced mammary tumors in rats when DDT, DDE, PCBs are given neonatally to rats.

### Question

**What is your level of confidence in scientists' ability to predict the effect of environmental exposure to DDT,DDE and PCB on breast cancer risk?**

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
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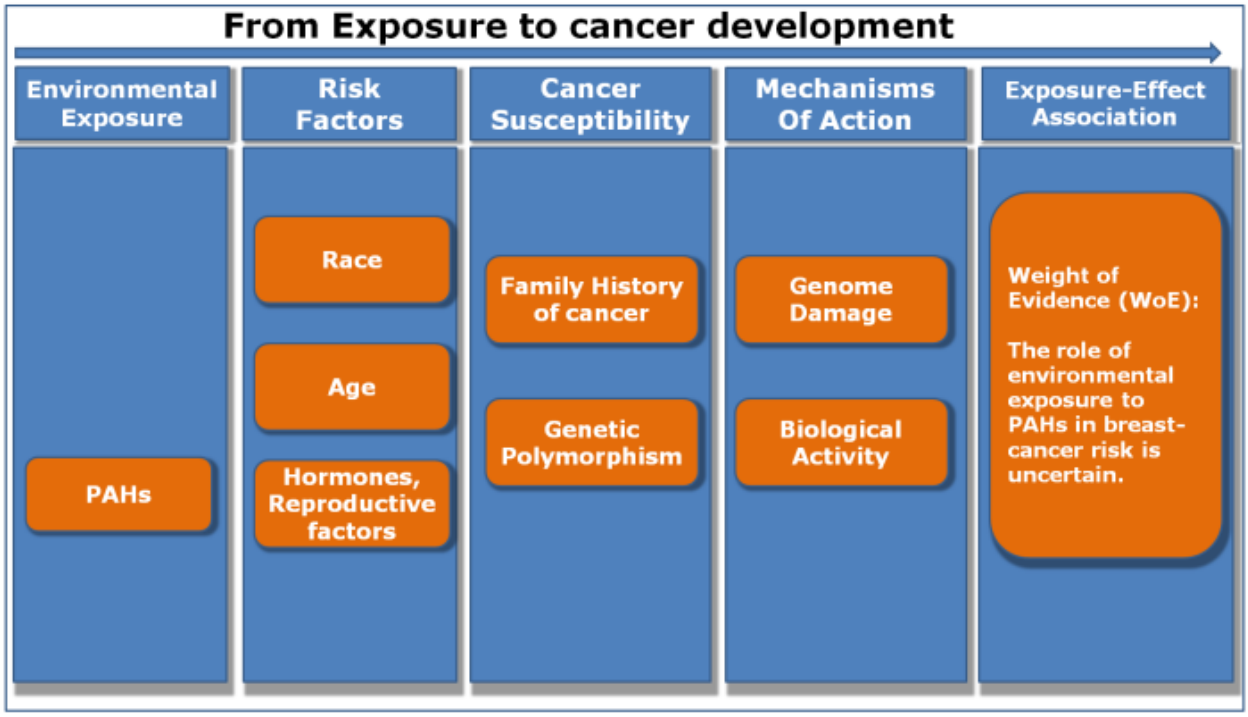
## Breast tumors - PAHs




**MECHANISMS OF ACTION**

*GENOME DAMAGE*

PAHs increase frequency of DNA adducts and chromosome damage

*BIOLOGICAL ACTIVITY*

Some PAHs are mammary carcinogens in laboratory animals. Poor evidence that PAHs interacted with GSTT1, GSTM1, GSTP1, and GSTA1 polymorphisms to increase breast cancer risk.

### Question

**What is your level of confidence in scientists' ability to predict the effect of environmental exposure to PHAs on breast cancer risk?**

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
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## Alcohol

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## PAH

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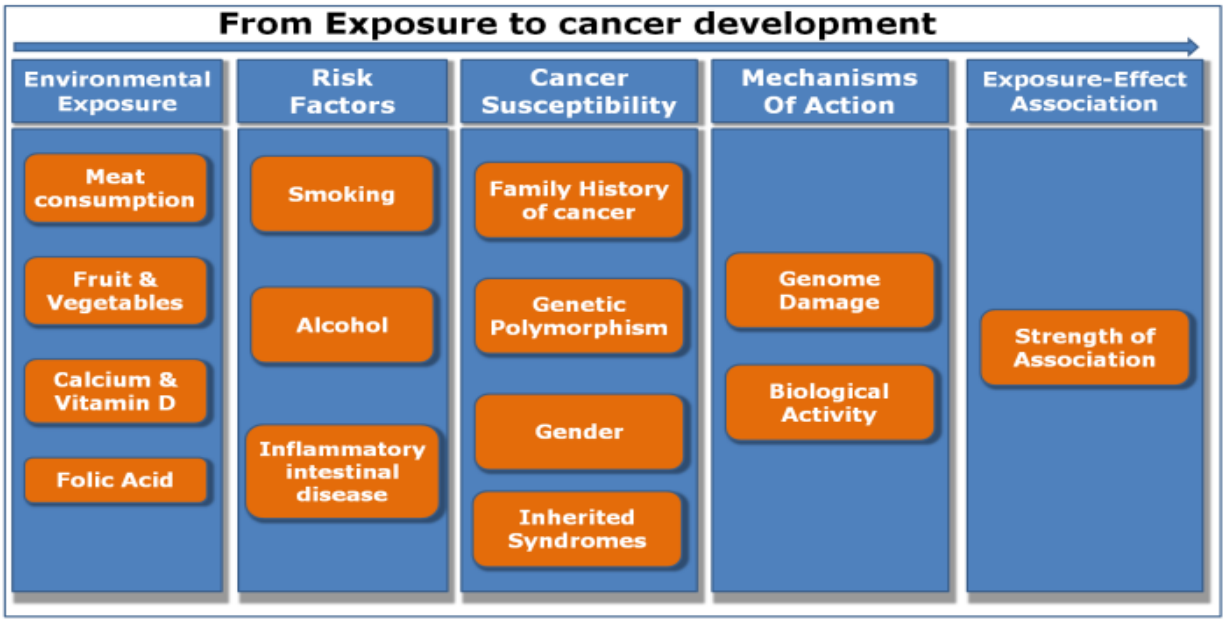
## Colorectal Tumors

- Adenocarcinoma (95%) of cases
  - Adenocarcinoma
  - Adenocarcinoma in adenomatous polyp
  - Adenocarcinoma in adenomatous polyposis coli
  - Adenocarcinoma in villous adenoma
- Mucinous adenocarcinoma
- Signet-ring cell carcinoma
- Lymphoma

**Localization**

- Right or proximal colon
  - Cecum
  - Ascending colon
  - Hepatic flexure
  - Proximal transverse colon (approximately the first two-thirds of the transverse)
- Left or distal colon
  - The last third of the transverse
  - Splenic flexure
  - Descending colon
  - Sigmoid colon
- Rectosigmoid
- Rectum



**RISK FACTORS (are valid for ALL exposures)**
*SMOKING*
CRC risk is increased in smokers.

*ALCOHOL*
A high alcohol intake is associated with an increased risk of colon cancer (RR=1.50 (1.25-1.79).

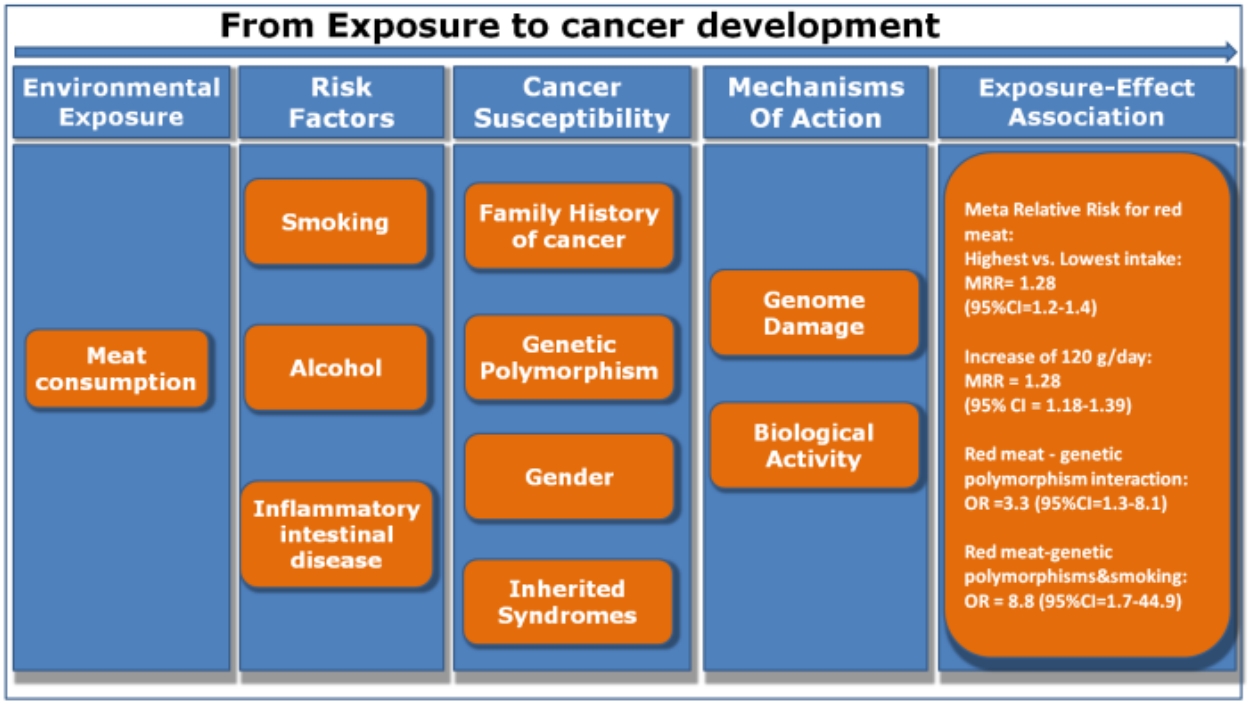
*INFLAMMATORY INTESTINAL DISEASE*
Risk of CRC doubles among patients with ulcerative colitis or Crohn's disease.

**CANCER SUSCEPTIBILITY (are valid for ALL exposures)**
*FAMILY HISTORY OF CANCER*
Family history of colon cancer in first-degree relatives
at least one relative: MOR=2.24 (2.06-2.43)
at least two relatives: MOR=3.97 (2.60-6.06)

*GENDER*
Incidence is higher in males than females

*INHERITED SYNDROMES*
Familial adenomatous polyposis (FAP) and hereditary non polyposis colorectal cancer (HNPCC) associated with lifetime increased risk of CRC.

## Colon – Meat consumption




***GENETIC POLYMORPHISMS***
CYP2E1, GSTA1, CYP1A2, NAT2 polymorphisms play an effect on susceptibility to CRC (OR=3.3; 95%CI:1.3-8.1)

**MECHANISMS OF ACTION**

*GENOME DAMAGE*

Chemical compounds produced during cooking can bind to macromolecules and DNA.

*BIOLOGICAL ACTIVITY*

Heterocyclic amines produced during cooking of red meat are suggested to cause CRC.

### Question

**What is your level of confidence in scientists' ability to predict the impact of red meat consumption on CRC risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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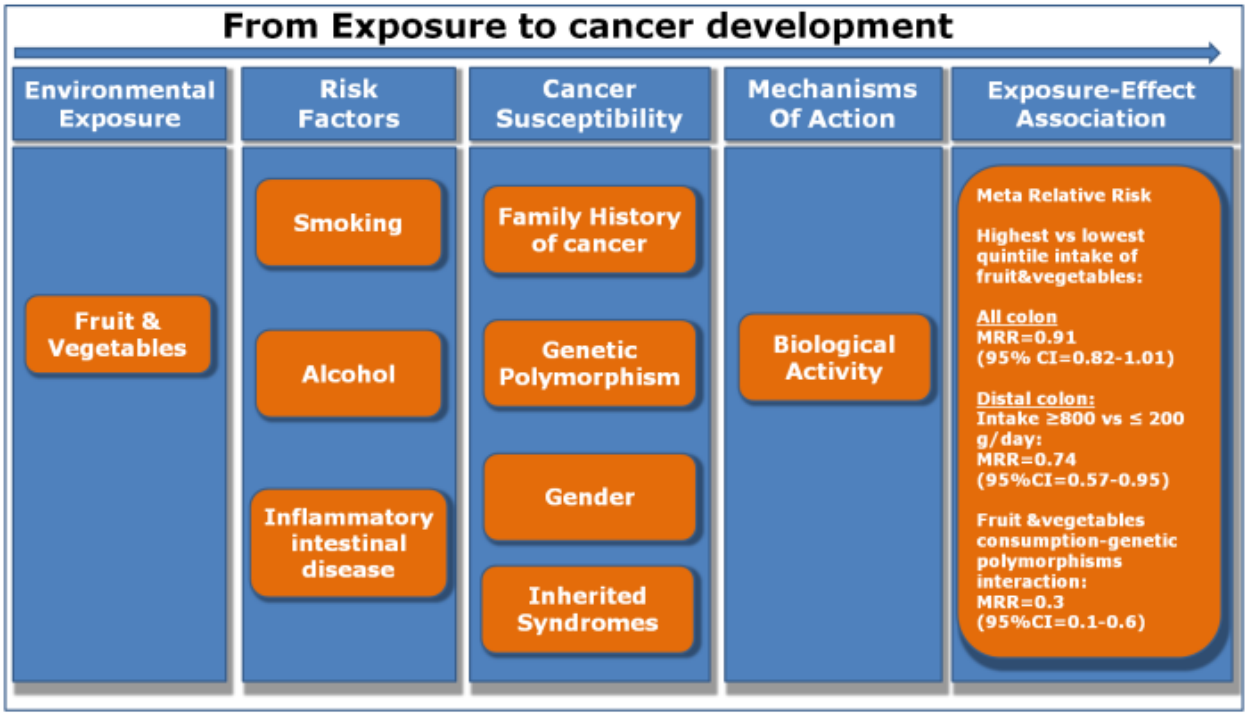
## Colon – Fruit and vegetables




***GENETIC POLYMORPHYSMS***

CYP2E1, CYP1A2, NAT2, GSTM1 and GSTT1 polymorphisms interact with high fruit and vegetable consumption to decrease colon cancer risk.

**MECHANISMS OF ACTION**

*BIOLOGICAL ACTIVITY*

Phytochemicals in fruits and vegetables have antioxidant activities. Additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for anticancer activity. The benefit of a diet rich in fruits and vegetables is attributed to phytochemicals present in whole foods.

### Question

What is your level of confidence in scientists' ability to predict the role of fruit and vegetables intake on CRC risk?

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
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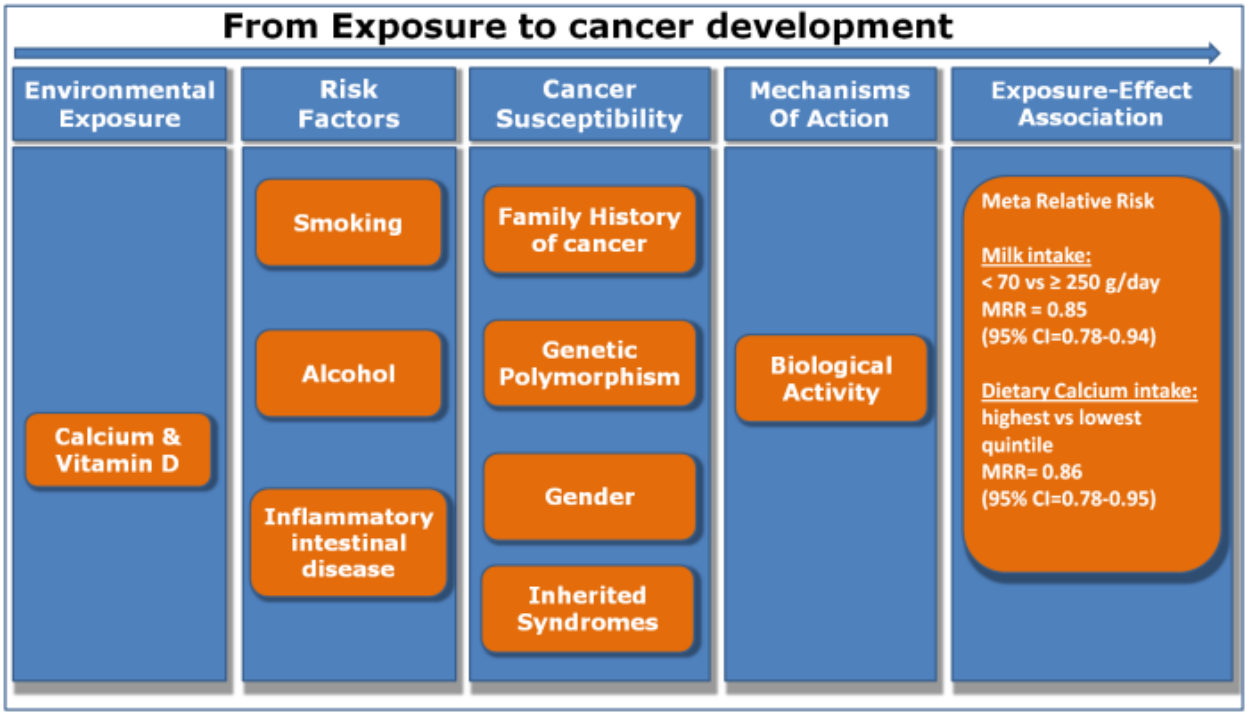
## Colon – Calcium and Vitamin D




**GENETIC POLYMORPHYSMS**

CYP2E1, CYP1A2, NAT2, GSTM1 and GSTT1 polymorphisms interact with high fruit and vegetable consumption to decrease colon cancer risk.

**MECHANISMS OF ACTION**

*BIOLOGICAL ACTIVITY*

Calcium and vitamin D are thought to reduce risk by decreasing cell proliferation or promoting cell differentiation.

### Question

What is your level of confidence in scientists' ability to predict the role of calcium and or Vitamin D intake on CRC risk?

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
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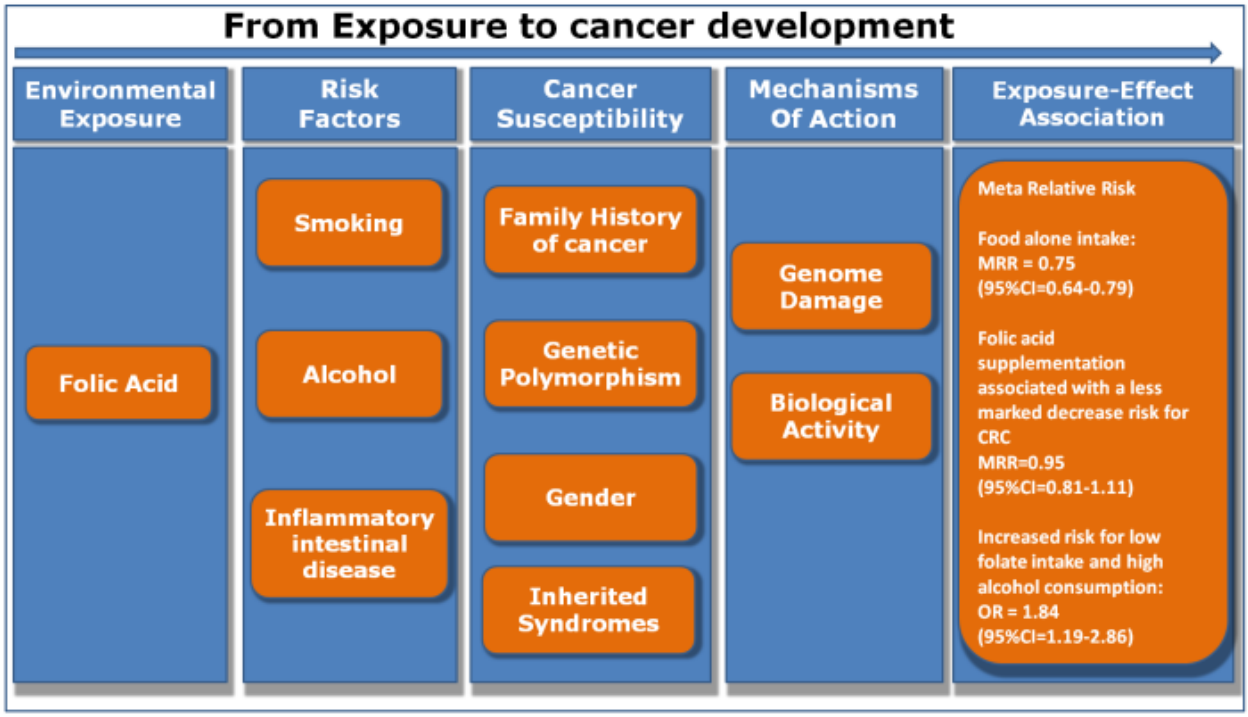
## Colon – Folic Acid




**GENETIC POLYMORPHYSMS**

Reduced risk in homozygotes with a variant form of the enzyme that regulates the conversion of folate.

**MECHANISMS OF ACTION**

*GENOME DAMAGE*

A low folate intake is associated with an increased frequency of chromosome breaks and micronucleated cells.

*BIOLOGICAL ACTIVITY*

Folate is a critical cofactor in biological methylation and nucleotide synthesis: a low folate level increases DNA methylation.

### Question

**What is your level of confidence in scientists' ability to predict the role of folic acid supplementation on CRC risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**What is your level of confidence in scientists' ability to explain the debate on the paradoxical role of folic acid intake on CRC risk (supplementation appears to be associated with a less marked decrease of risk for CRC)?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
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| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
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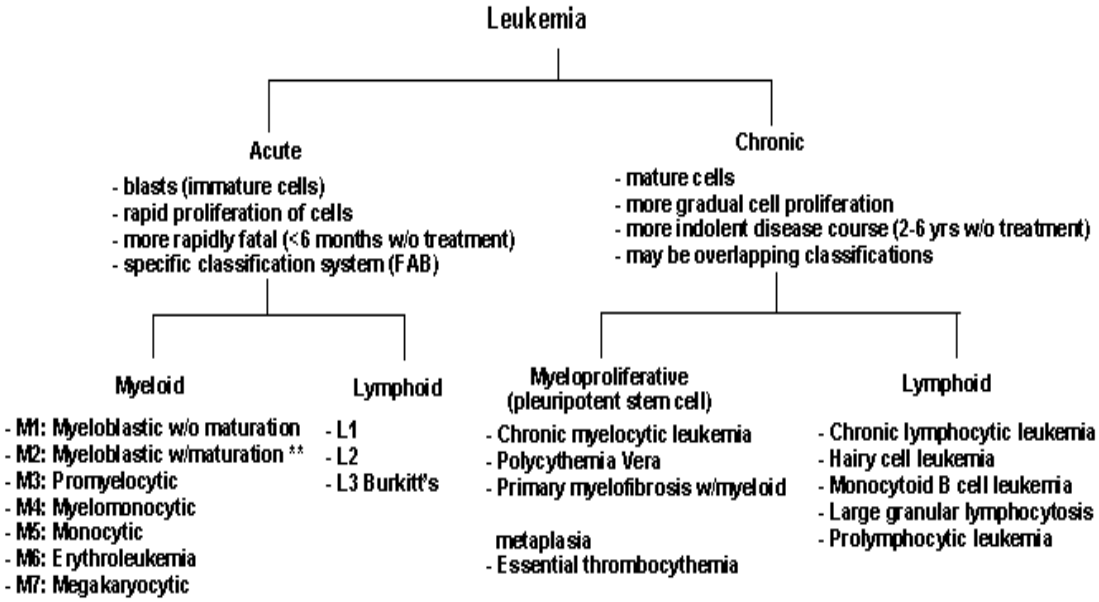
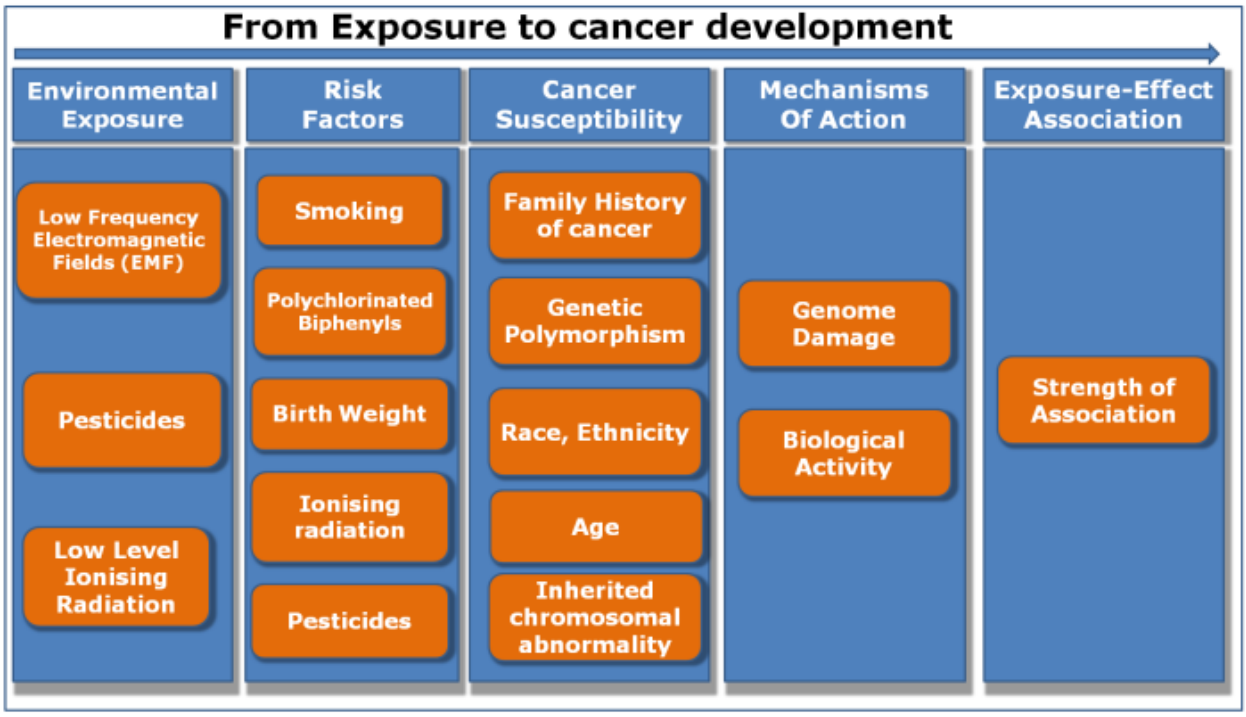
## Leukemia

A progressive, malignant disease of the blood-forming organs. It is characterized by overproduction of white blood cells and their precursors in the blood and bone marrow.
Leukaemia is classified according to degree of cell differentiation as **acute** or **chronic,** and according to predominant type of cell involved as **myelogenous** or **lymphocytic**.




**RISK FACTORS (apply for ALL exposures)**
*SMOKING*
Cigarette smoke contains leukemia-causing chemicals (e.g., benzene). One in four cases of acute myelogenous leukemia (AML) is attributed to cigarette smoking.

*POLYCHLORINATED BIPHENYLS*
PCBs may represent a risk factor for childhood leukemia (they are probable human carcinogens and cause perturbations of the immune system).

*BIRTH WEIGHT*
High birth weight may be associated with an increased risk of overall leukemia and acute lymphocytic leukemia (ALL).

*IONIZING RADIATION*
People who have been exposed to high doses of ionizing radiation (i.e., atomic bomb survivors) have a high risk of chronic myelogenous leukemia (CML).

P*ESTICIDES*
Increased risks have been reported in workers exposed to herbicides, and pesticides, particularly for chronic lymphocytic leukemia (CLL).

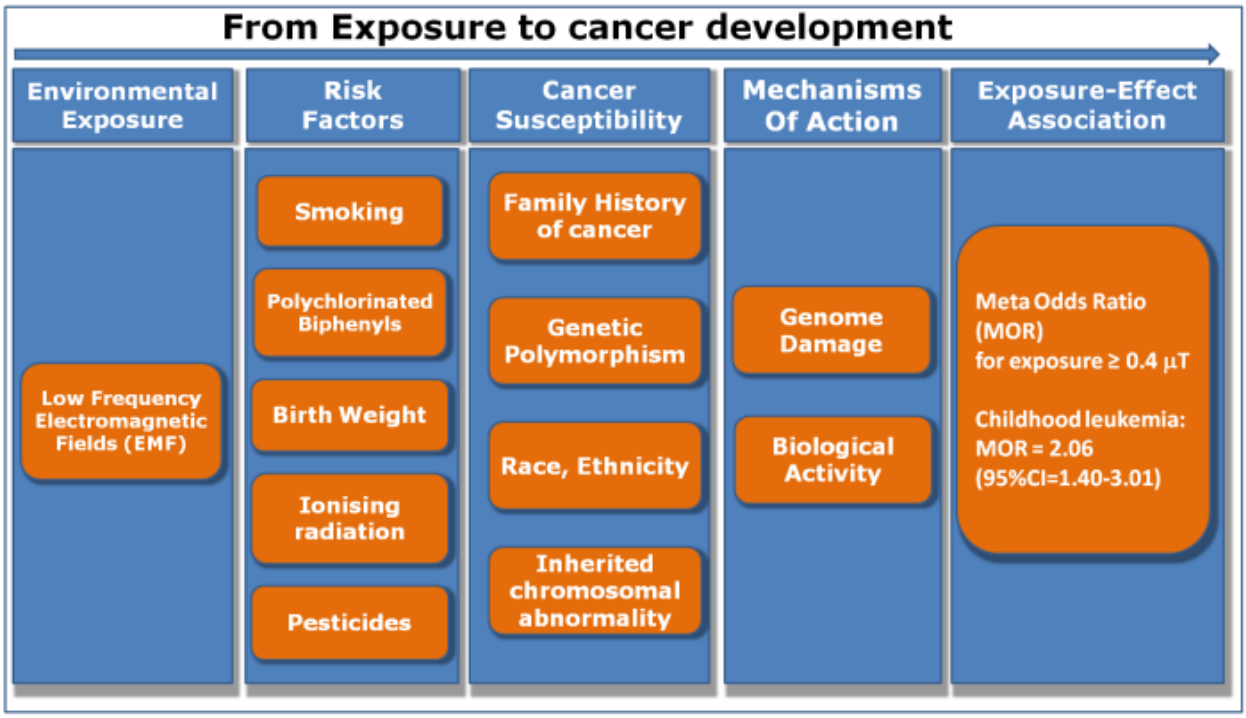
**CANCER SUSCEPTIBILITY (apply for ALL exposures)**
*FAMILY HISTORY OF CANCER*
First-degree relatives of chronic lymphocytic leucemia (CLL) patients have an increased risk for this cancer.

*GENETIC POLYMORPHYSMS*
Increased risk in children carrying the the CYP1A1m1 and CYP1a1m2 mutations exposed to indoor insecticides.
Several low-penetrance genes (CYP, NQO1, GSTT1, GSTM1, GSTP1, MTHFR, TYMS, SHMT1, MTRR, XPD, XPG, RAD51, XRCC1, XRCC3, CHEK2, ATM) may account for the risk of leukaemia via gene-environment interaction.

*RACE, ETNICITY*
Rates of leukemia (e.g., CLL) are elevated in some Jewish populations and low in Asian populations.

*INHERITED CHROMOSOMAL ABNORMALITY*
Children with Down's syndrome have a higher risk of leukemia. Other inherited disorders (Fanconi's anemia, Bloom's syndrome, and ataxia telangiectasia) have an increased risk for leukemia.

## Leukemia – Electromagnetic Fields (EMF)




**MECHANISMS OF ACTION**

*GENOME DAMAGE*

EMF do not have sufficient energy to affect DNA molecules, but even weak electric and magnetic fields can cause changes in charge distribution that trigger large structural changes in proteins.

*BIOLOGICAL ACTIVITY*

Weak EMF can control and amplify biological processes through their effects on charge distribution.

### Questions

**What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to residential low frequency electromagnetic fields and the risk of leukaemia in children?**

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
|---|---|---|---|---|
| | | | | |

**What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to residential electromagnetic fields on leukaemia risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce EMF exposure?**

In favor ☐ Against ☐

**If you have any specific policy actions in mind, please specify them here:**

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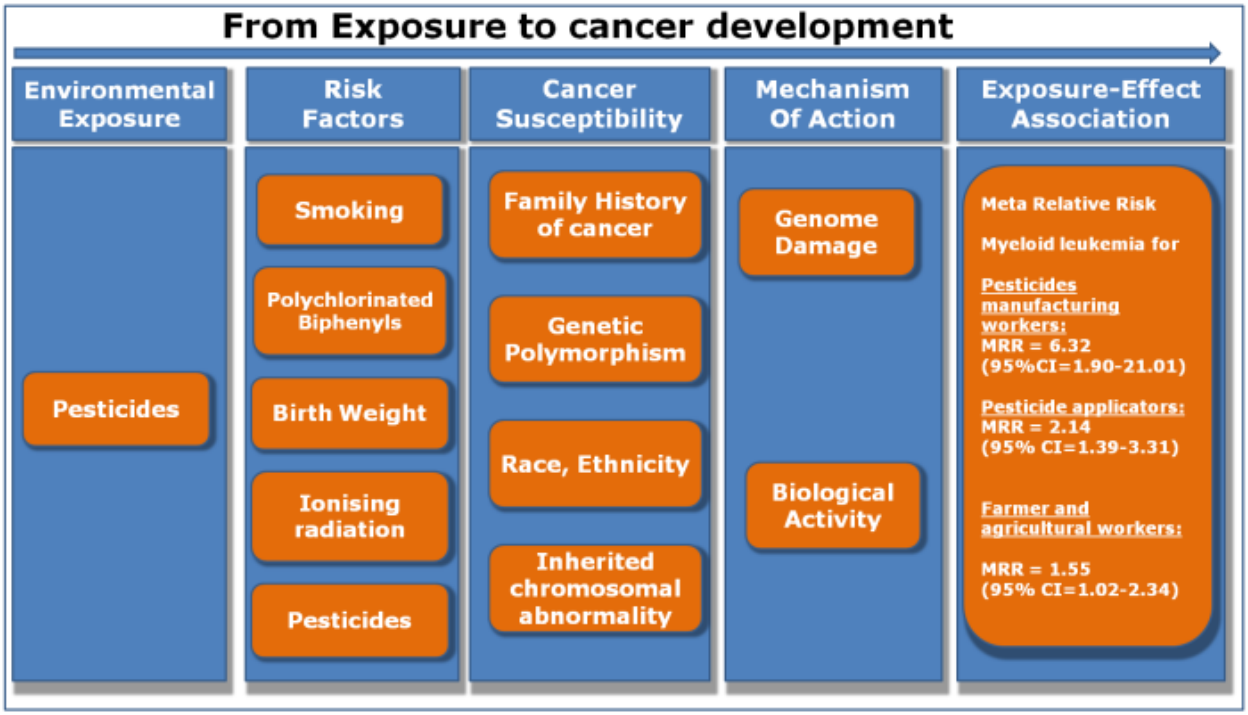
## Leukemia - Pesticides



**MECHANISMS OF ACTION**

*GENOME DAMAGE*

Chromosome aberrations and increased frequency of micronuclei have been detected in the majority of studies, mitotic arrest, clastogens, aneugens, some pesticides cause disturbances of mitotic spyndle

*BIOLOGICAL ACTIVITY*

Translocations or clonotypic gene fusion sequences match that of later leukemic blasts in blood spots (Guthrie card); some pesticides are xenoestrogens, ROS production.

## Questions

**What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to pesticides and the risk of leukaemia?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to pesticides on leukaemia risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

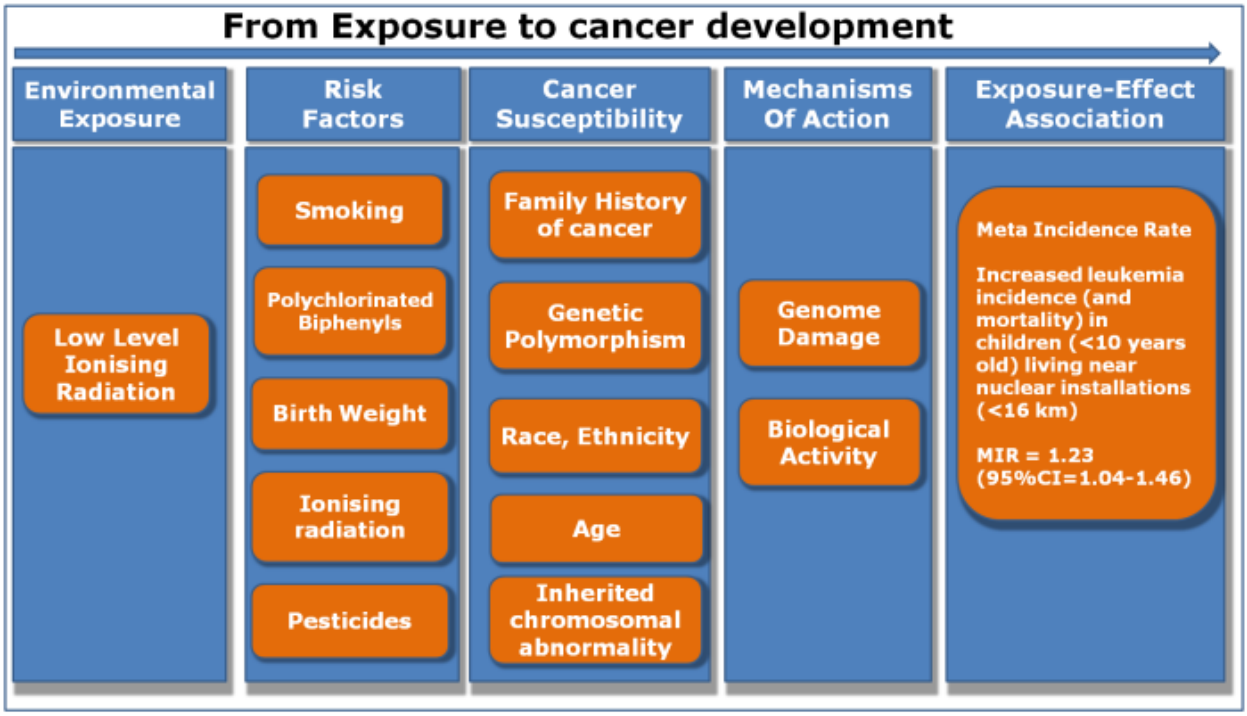
**Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce pesticides exposure?**

In favor ☐ Against ☐

**If you have any specific policy actions in mind, please specify them here:**

| |
|---|
| |

## Leukemia – Low Level ionising radiation




**MECHANISMS OF ACTION**

*GENOME DAMAGE*

Chromosome aberrations and increased frequency of micronuclei have been detected in the majority of studies.

*BIOLOGICAL ACTIVITY*

Translocations or clonotypic gene fusion sequences match that of later leukemic blasts in blood spots (Guthrie card); ROS production; damage DNA, RNA, proteins by breaking chemical bonds and cross-linking between macromolecules, inducing methylation disturbances.

### Questions

**What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to low level ionising radiation and the risk of leukaemia?**

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
|---|---|---|---|---|
| | | | | |

**What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to low level ionising radiation on childhood leukaemia risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce exposure to ionising radiation?**

In favor ☐ Against ☐

**If you have any specific policy actions in mind, please specify them here:**

| |
|---|
| |

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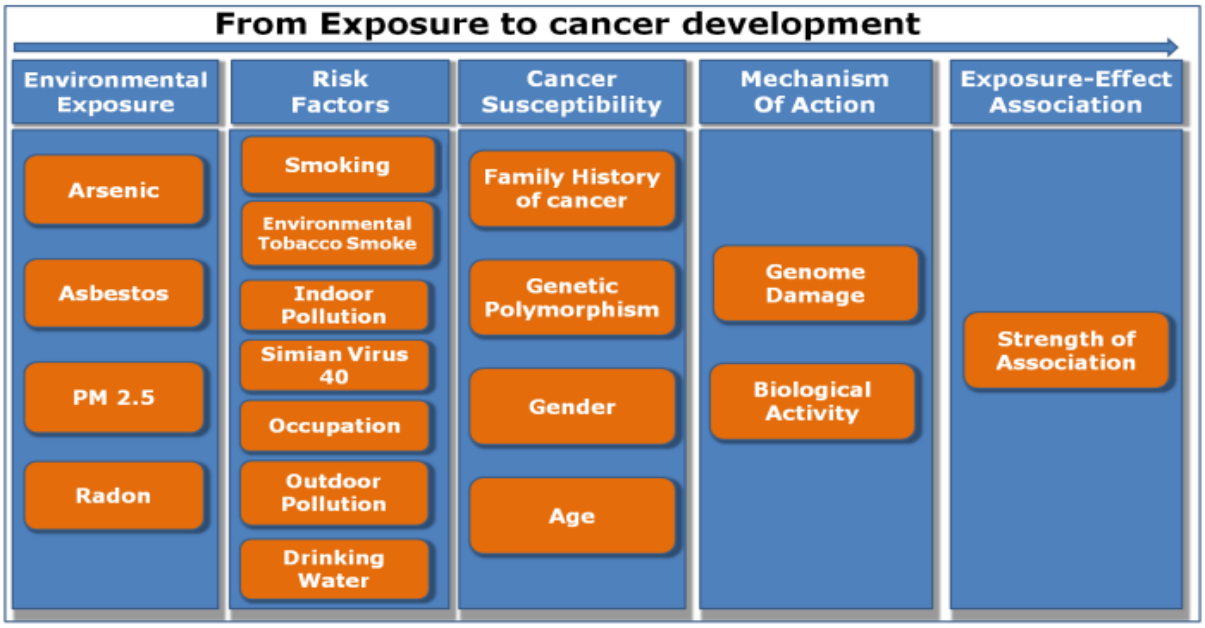
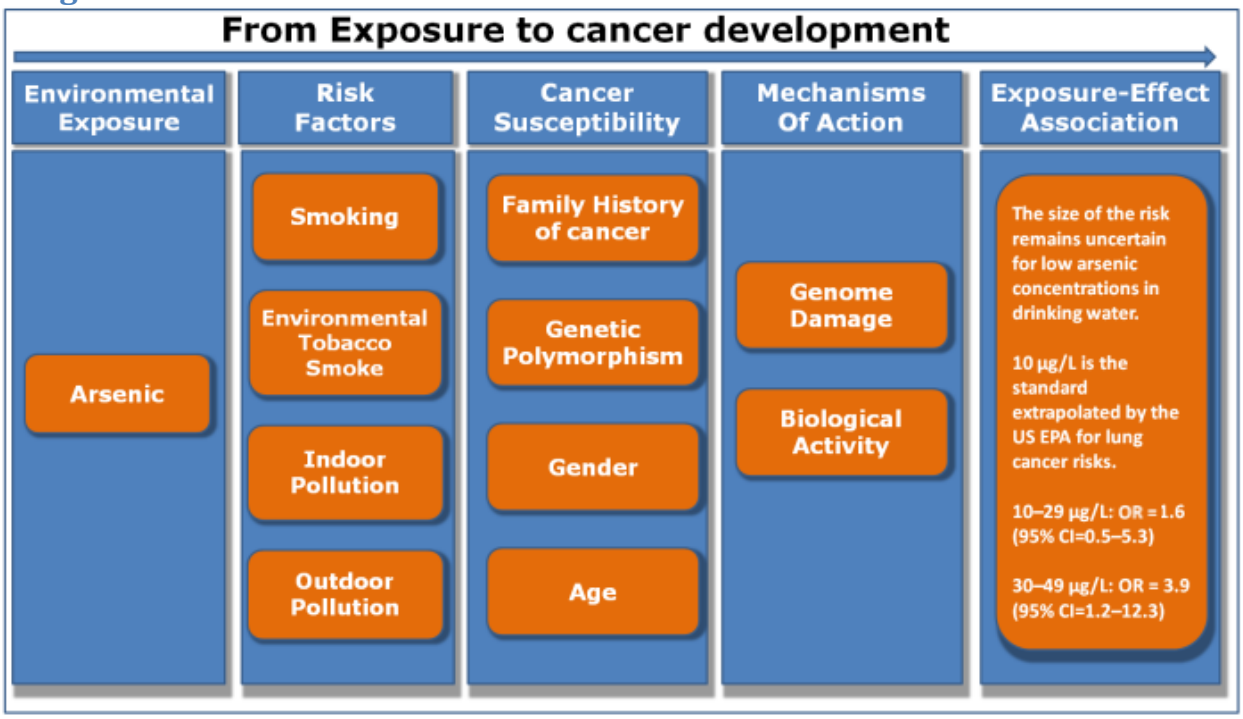
## Lung Mesothelioma




| TYPES OF MALIGNANT PLEURAL MESOTHELIOMA | TYPES OF LUNG TUMORS |
|---|---|
| ▪ Epithelial<br>▪ Sarcomatoid<br>▪ Desmoplastic<br>▪ Biphasic or mixed<br><br>Approximately 60% of MPM cases have epithelial histology, 30% biphasic or mixed, and the remaining 10% sarcomatoid. Biphasic tumors must have both epithelioid and sarcomatoid components, with the minor component representing at least 10% of the tumor area. | ▪ Malignant epithelial lung tumors<br>• Squamous cell carcinoma<br>• Small cell carcinoma<br>• Adenocarcinoma<br>• Large cell carcinoma<br>• Adenosquamous carcinoma<br>• Sarcomatoid carcinoma<br>• Carcinoid tumour<br>• Salivary Gland Tumors<br>• Preinvasive lesions<br>• Mesenchymal tumours<br>▪ Benign epithelial tumours<br>▪ Lymphoproliferative tumours<br>▪ Metastatic tumours<br>▪ Others |

From a clinical and prognostic standpoint, lung carcinomas are broadly divided into non small cell carcinoma (NSCLC) and small cell carcinoma (SCLC), accounting for 20-25% of all lung carcinomas. NSCLCs traditionally include three major types: adenocarcinoma, squamous cell carcinoma (SSC) and large cell carcinoma, but in the broadest sense may include any epithelial tumor that lacks a small cell component.

## Lung – Arsenic




**RISK FACTORS**

*SMOKING*

Smoking is the major risk factor for lung cancer.
Arsenic and cigarette smoke synergistically increase DNA oxidation in the lung.

*ENVIRONMENTAL TOBACCO SMOKE*

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

*INDOOR POLLUTION*

Lung cancer may be associated with indoor pollution from heating an cooking with solid fuels.
Indoor radon is associated with an increased lung cancer risk.

*OUTDOOR POLLUTION*

Combustion products from fossil fuels containing carcinogenic PAHs (e.g., diesel exhaust).
The component with the greatest public impact is probably $PM_{2.5}$: RR increase range between 15% and 21% for a 10 µg/$m^3$ increase in $PM_{2.5}$ air level.
Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6)

**CANCER SUSCEPTIBILITY**

*FAMILY HISTORY OF CANCER*

Systematic reviews have shown a relationship between family history and lung cancer risk (Meta RR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

*GENETIC POLYMORPHISMS*

GSTM1 may have an important role in As methylation capacity and body retention.
A susceptibility locus for lung cancer: nicotinic acetylcholine receptor subunit genes
Carriers of the GSTM1 null genotype have an increased lung cancer risk: MOR=1.64 (95%CI=1.25-2.14); carriers of the GSTT1 null genotype: MOR= 1.49 (95%CI=1.17-1.89).

*GENDER*
Female smokers are at higher risk for lung cancer than male smokers. Endocrine factors may play a role in adenocarcinoma of the lung in women.

*AGE*
Exposure in utero and early childhood to carcinogenic agents may lead to increased lung cancer risk later in life.

**MECHANISMS OF ACTION**
*GENOME DAMAGE*
Arsenic metabolites methylarsonic acid (MMA) and dimethylarsinic acid (DMA) are cytotoxic and genotoxic in cell lines (chromosomal abnormalities, oxidative stress); MMA is metabolised to DMA and both compounds are classified as "possibly carcinogenic to humans" (Group 2B).

*BIOLOGICAL ACTIVITY*
Arsenic causes oxidative DNA damage, genomic instability, aneuploidy, gene amplifi cation, epigenetic effects. DNA methylation of specific genes are associated with risk factors and gender; DNA-repair inhibition leads to mutagenesis.

## Questions

**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to arsenic in drinking water on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

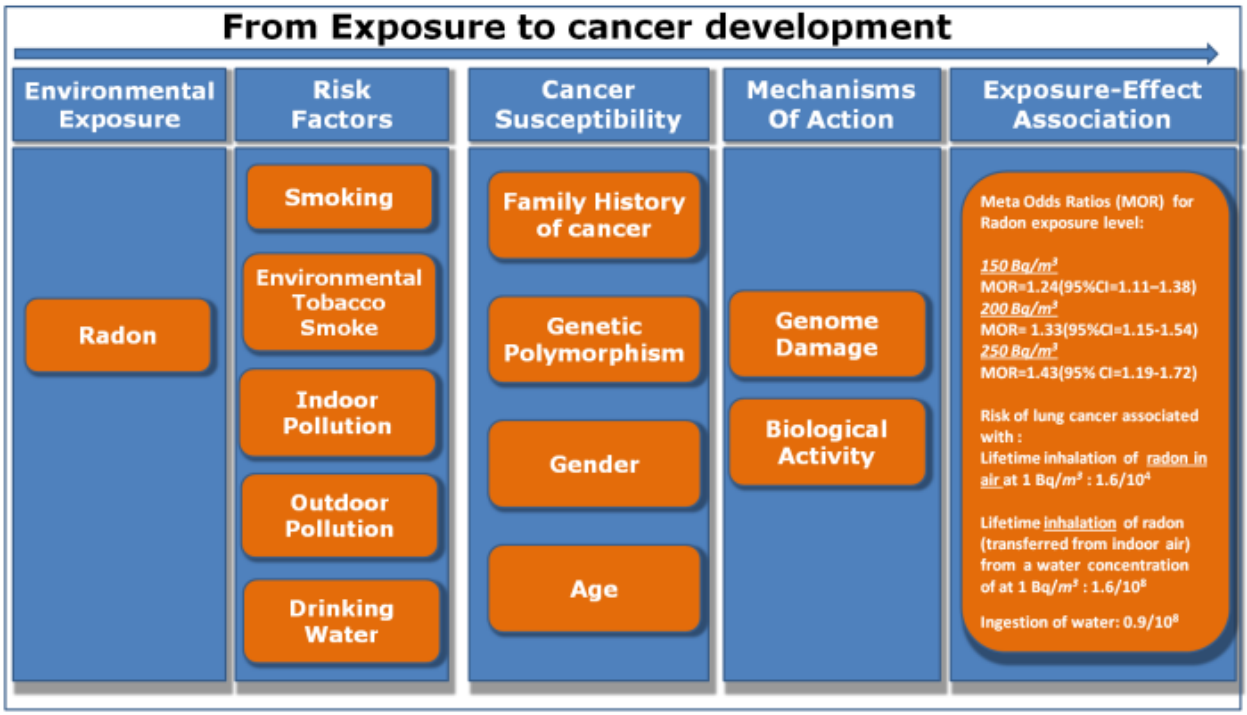
**What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between arsenic in drinking water and smoking on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and early childhood exposure to arsenic in drinking water on lung cancer risk?

| Very high confidence.<br><br>At least 9 in 10 chance of being correct | High confidence.<br><br>At least 7 in 10 chance of being correct. | Medium confidence.<br><br>At least 5 in 10 chance of being correct. | Low confidence.<br><br>At least 3 in 10 chance of being correct. | Very low confidence.<br><br>Less than 2 out of 10 chance of being correct. |
|---|---|---|---|---|
| | | | | |

## Lung - Radon




**RISK FACTORS**

*SMOKING*

Smoking is the major risk factor for lung cancer.

Smoking exerts a supra additive effect on Radon-induced lung cancer risk.

*ENVIRONMENTAL TOBACCO SMOKE*

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

*INDOOR POLLUTION*

Lung cancer may be associated with indoor pollution from heating and cooking with solid fuels.

*OUTDOOR POLLUTION*
Combustion products from fossil fuels contains carcinogenic PAHs.The component with the greatest public impact is probably $PM_{2.5}$: RR increase range between 15% and 21% for a 10 μg/$m^3$ increase in PM2.5 air level. Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6)

*DRINKING WATER*
Ingesting drinking water with high concentrations of arsenic is associated with lung cancer risk.

**CANCER SUSCEPTIBILITY**
*FAMILY HISTORY OF CANCER*
Systematic reviews have shown a relationship between family history and lung cancer risk
(Meta RR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

*GENETIC POLYMORPHISMS*
A susceptibility locus for lung cancer: nicotinic acetylcholine receptor subunit genes.
Carriers of the GSTM1 null genotype have an increased lung cancer risk. MOR=1.64 (95%CI=1.25-2.14); carriers of the GSTT1 null genotype: MOR= 1.49 (95%CI=1.17-1.89)

*GENDER*
Female smokers are at higher risk for lung cancer than male smokers.
Endocrine factors may play a role in adenocarcinoma of the lung in women.

*AGE*
Exposure in utero and early childhood to carcinogenic agents may lead to increased lung cancer risk. later in life

**MECHANISMS OF ACTION**
*DNA DAMAGE*
Radon induces chromosome damage at very low doses (dicentrics, acentric fragments and centric rings); increases the frequency of micronuclei in in vitro exposed human lymphocytes.

*BIOLOGICAL ACTIVITY*
Radon alpha particles create dense ionization: cells nucleus are severely injured by particles track. Injuries include gene deletions, rearrangements, amplifications, persistant genomic instability, mutations in oncogenes, loss of function in tumor suppressors, all contributing to malignant transformation.

## Questions

**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to Radon on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

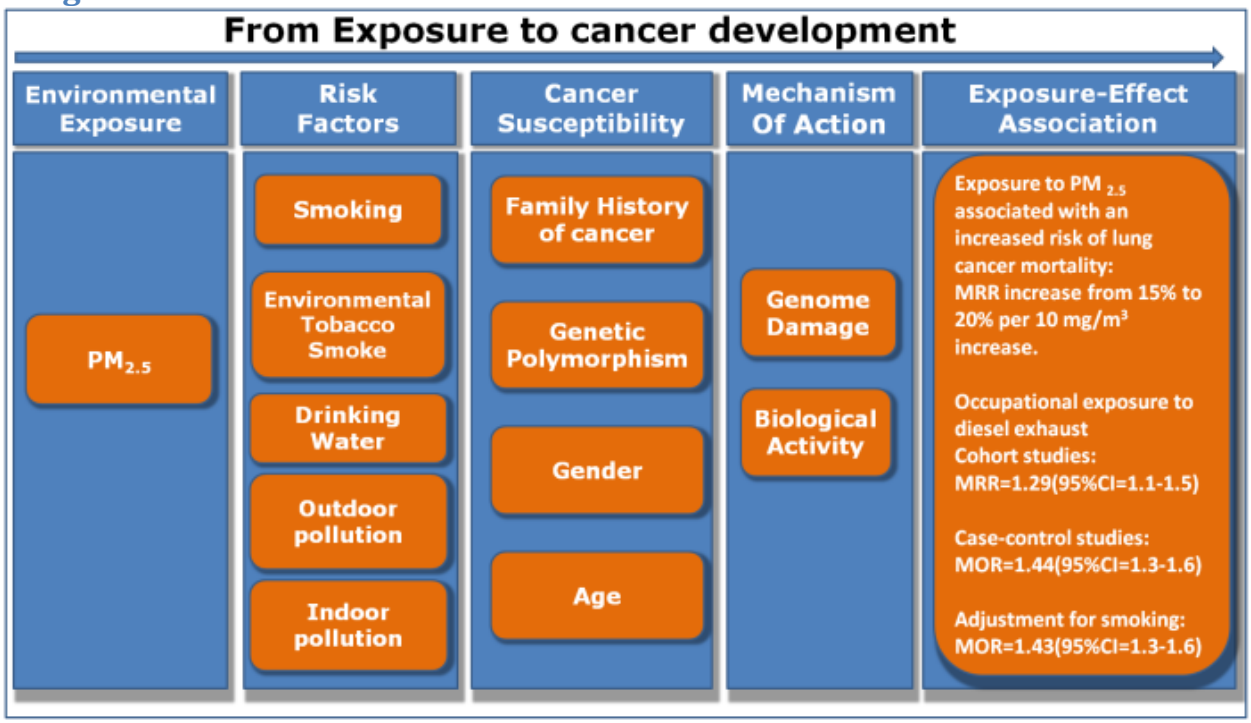
**What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between Radon exposure and smoking on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and early childhood exposure to Radon on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

## Lung – PM 2.5




**RISK FACTORS**

*SMOKING*

Smoking is the major risk factor for lung cancer.

*ENVIRONMENTAL TOBACCO SMOKE*

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

*DRINKING WATER*

Ingesting drinking water with high concentrations of arsenic is associated with lung cancer risk.

*OUTDOOR POLLUTION*

Combustion products from fossil fuels contains carcinogenic PAHs.
Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6).

*INDOOR POLLUTION*

Lung cancer may be associated with indoor pollution from heating and cooking with solid fuels
Indoor radon is associated with an increased lung cancer risk.

**CANCER SUSCEPTIBILITY**

*FAMILY HISTORY OF CANCER*

Systematic reviews have shown a relationship between family history and lung cancer risk (Meta RR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

*GENETIC POLYMORPHISMS*
Air pollutants (e.g., PAHs) require metabolic activation to exhert genotoxicity and to be excreted: phase I and phase II metabolic genes polymorphism may increase cancer risk.
Carriers of the GSTM1 null genotype have an increased lung cancer risk. MOR=1.64 (95%CI=1.25-2.14); carriers of the GSTT1 null genotype: MOR= 1.49 (95%CI=1.17-1.89).
*GENDER*
Female smokers are at higher risk for lung cancer than male smokers.
Endocrine factors may play a role in adenocarcinoma of the lung in women.

*AGE*
Exposure in utero and early childhood may increase the risk of lung cancer development later in life.

**MECHANISMS OF ACTION**
*DNA DAMAGE*
Indoor and outdoor agents have genotoxic properties and induce oxidative stress.

*BIOLOGICAL ACTIVITY*
Fuel combustion products contain carcinogens. It is not clear whether PM2.5 possesses carcinogenic properties beyond those of the known chemical carcinogens which it contains (PAH, Cr, Ni, and As). Coal combustion increases indoor levels of PAHs, benzene, arsenic, and formaldehyde. Peanut oil, when heated, releases mutagenic compounds and soybean, sunflower, rapeseed oil, and lard have genotoxic properties and induce oxidative stress.

## Questions

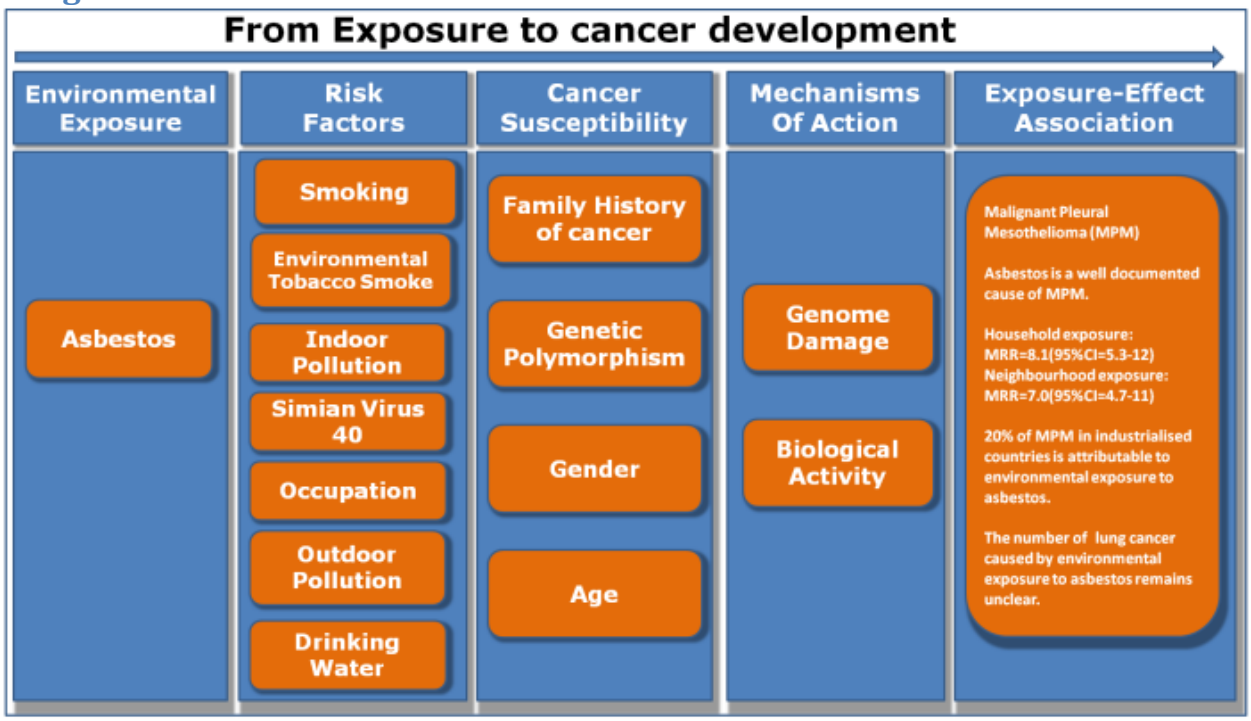
**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to PM2.5 on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**What is your level of confidence in scientists' ability to predict the magnitude of the effect of indoor heating and cooking with solid fuels on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

## Lung – Asbestos




**RISK FACTORS**

*SMOKING*

Smoking does not increase the risk of MPM, but is the major risk factor for lung cancer.
There is a synergistic effect between asbestos and tobacco smoking in lung cancer risk.
The excess relative risk of lung cancer from asbestos exposure is about three times higher in non-smokers than in smokers.

*ENVIRONMENTAL TOBACCO SMOKE*

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

*INDOOR POLLUTION*

Lung cancer may be associated with indoor pollution from heating and cooking with solid fuels.
Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6).

*SIMIAN VIRUS 40 (SV40)*

SV40 was found in 1960 in kidney cells of rhesus macaque monkey that were used in the production of the polio vaccines. Infants vaccinated with the SV40 contaminated poliovirus vaccine may have increased risk of mesothelioma and other cancers. The scientific evidence is insufficient to prove or disprove a causal role of poliovirus vaccine contaminated with SV40.

OCCUPATION

Working with asbestos (occupational exposure) is the major risk factor for MPM. Lung cancer risk increases with increasing duration of exposure to asbestos.

*OUTDOOR POLLUTION*
Outdoor air pollution is suspected of increasing the risk of lung cancer. The component with the greatest public impact is probably PM2.5: RR increase range between 15% and 21% for a 10 μg/m3 increase in PM2.5 air level. Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6)

DRINKING WATER
Ingesting drinking water with high concentrations of arsenic is associated with lung cancer risk.

**CANCER SUSCEPTIBILITY**
*FAMILY HISTORY OF CANCER*
Systematic reviews have shown a relationship between family history and lung cancer risk (MRR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

*GENETIC POLYMORPHISMS*
The polymorphic metabolic/oxidative enzyme myeloperoxidase (MPO) genotypes modify the effect of asbestos exposure on lung cancer risk: OR=1.72 (95% CI; 1.09-2.66)
The polymorphism of other genes are associated to an increased risk of MPM
GSTM1: OR= 1.69 (95%CI =1.04-2.74), MnSOD: OR= 3.07. 95% CI = 1.55-6.05), XRCC1-399Q: 2.38 (95% CI=0.82-6.94)

*GENDER*
Female smokers are at higher risk for lung cancer than male smokers

*AGE*
Exposure in utero and early childhood to carcinogenic agents may lead to increased lung cancer risk later in life

**MECHANISMS OF ACTION**
*GENOME DAMAGE*
Chromosomes are damaged by asbestos when cells divide. Mitochondria are targets of asbestos-induced DNA damage and apoptosis via an oxidant-related mechanism. Impaired fibre clearance leads to macrophage activation, infl ammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signalling pathways, resistance to apoptosis

*BIOLOGICAL ACTIVITY*
Asbestos act as a carcinogen by generating free radicals and reactive oxygen species, inducing tissue injury and subsequent cellular growth. Asbestos fibers may concentrate chemical carcinogens including the components of cigarette smoke. Asbestos enhances the mutagenicity of tobacco carcinogens.

## Questions

**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to asbestos on MPM risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to asbestos on lung cancer risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
| | | | | |

**What is your level of confidence in scientists' ability to assess the role and the magnitude of exposure to Simiam virus vaccination on MPM risk?**

| Very high confidence. | High confidence. | Medium confidence. | Low confidence. | Very low confidence. |
|---|---|---|---|---|
| At least 9 in 10 chance of being correct | At least 7 in 10 chance of being correct. | At least 5 in 10 chance of being correct. | At least 3 in 10 chance of being correct. | Less than 2 out of 10 chance of being correct. |
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## Asbestos –MPM and LUNG CANCER

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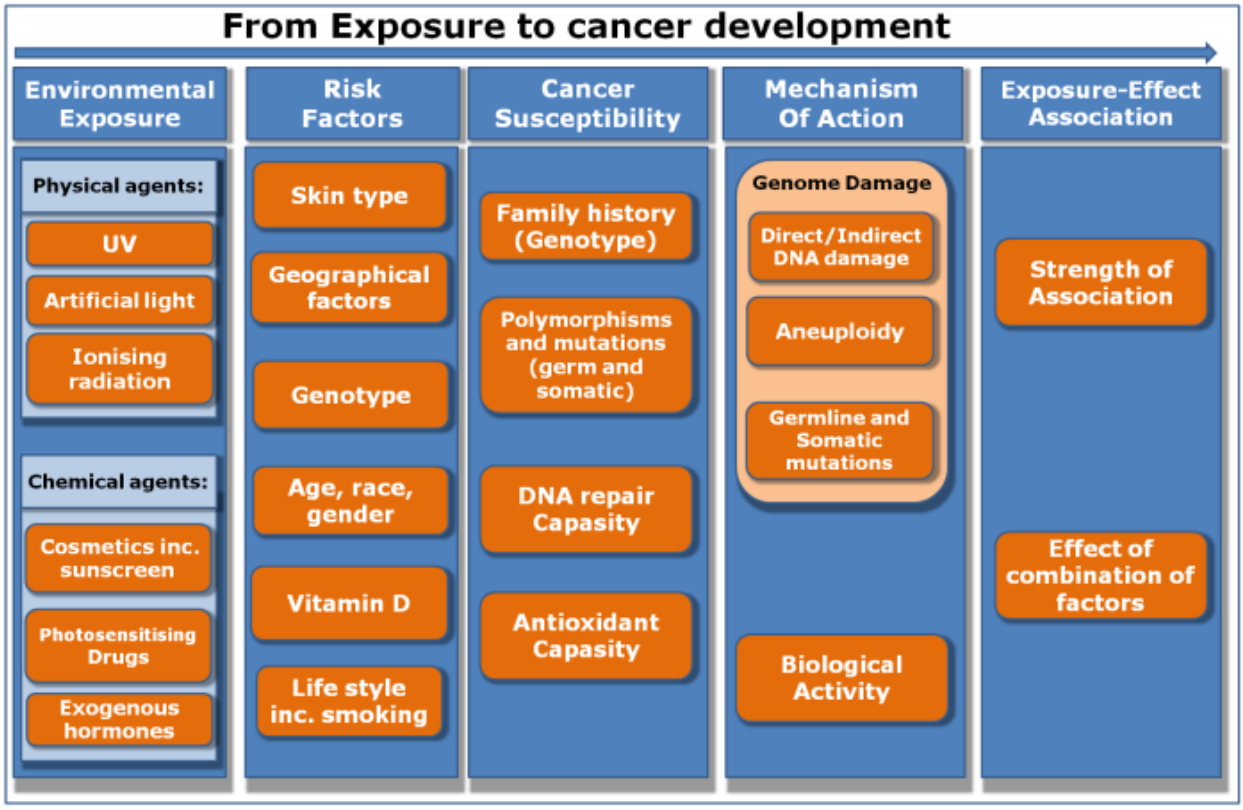
## Melanoma




Malignant tumor of melanocytes accounts for 90% of skin cancer mortality arises from dendritic melanocytes in the skin, (eyes, mucosa, meninges). Incidence of melanoma is dramatically increasing. While in US the lifetime risk of melanoma in 1935 was 1 in 1,500 persons, in 1960, 1 in 600 persons, lifetime risk of melanoma in 2000 was 1 in 75 persons .

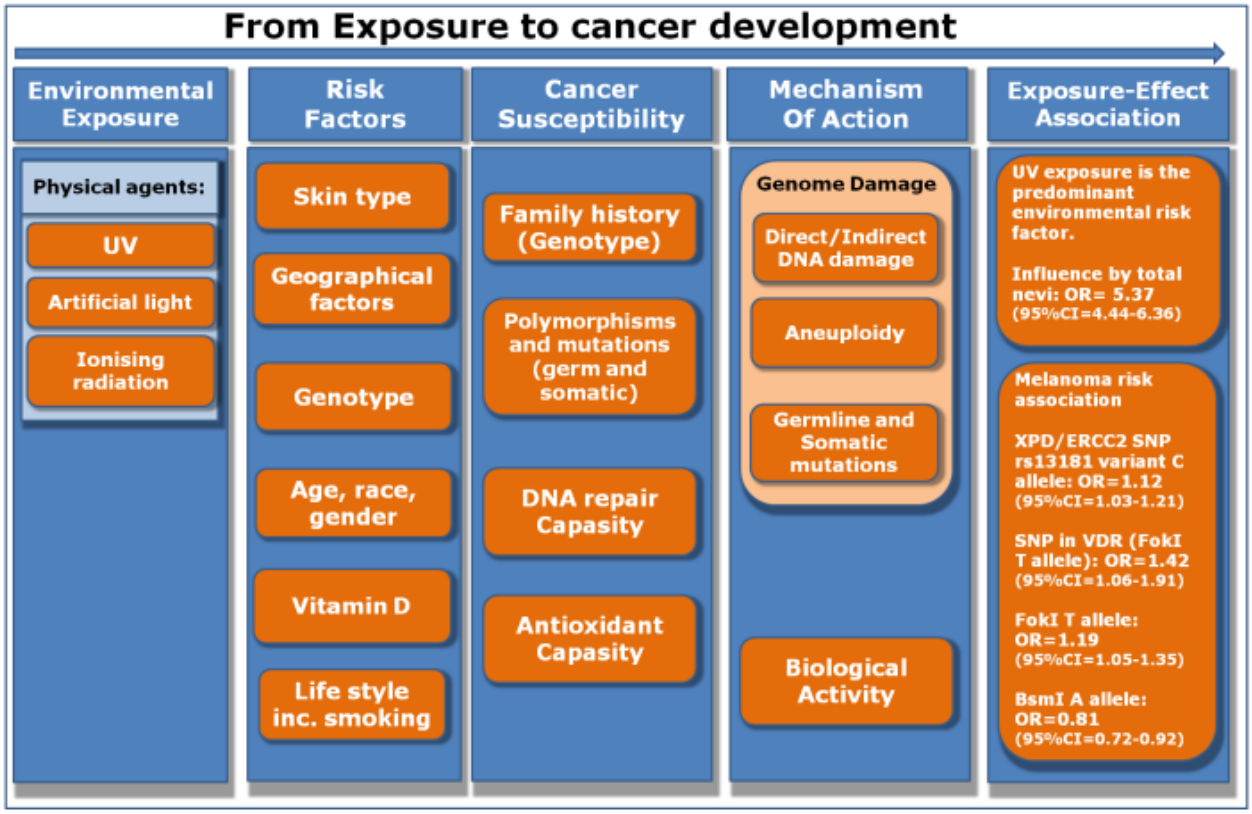
Types of Melanoma:

- Superficial spreading melanoma (about 70% of diagnosed cases) – any age (middle aged)
- Nodular melanoma (about 15% of diagnosed cases) – middle aged
- Lentigo maligma melanoma (about 10% of diagnosed cases) – middle aged, elderly
- Acral lentigous melanoma (about 5% of diagnosed cases) – Asian and dark skin
- Melanoma of the skin - cutaneous .

Melanoma can occur anywhere in the body, including in the internal organs.

### Melanoma - Physical agents

Physical agents: (UV, artificial light, ionising radiation): Among the risk factor the sun-exposure (intermittant exposure, exposure in childhood) is one of the major risk factors in occurrence of melanoma. High exposure in the childhood combined with high exposure in adult life give a high risk of melanoma.




**RISK FACTORS**

*SKIN TYPE*

Malignant melanoma mainly afflicts people with white skin (Caucasian population). Risk of melanoma depends on skin type. Particularly dysplastic nevi confer much higher risks than most pigmentary characteristics.

*GEOGRAPHICAL FACTORS*

Sun exposure plays a primary and supporting role in most melanoma tumors. UV radiation exposure is the predominant environmental risk factor for melanoma. Melanoma incidence varies across countries, depending on differences in UV radiation in different geographical regions.

*GENOTYPE*

Approximately 10% of melanoma is inherited (Familial). About 40 percent of familial melanoma is associated with chromosome 9p. There are geographical variation in the penetrance of the melanoma susceptibility genes CDK4 and CDKN2A mutations.

*RACE, GENDER AND AGE*

Malignant melanoma mainly afflicts Caucasian population. Among cases aged 15-30 years, females have a higher melanoma risk; after age 30, incidence is higher among males. Generally older age and male gender are associated with prognostically unfavorable primary cutaneous melanoma.

*VITAMIN D*

Indoor solar UVA exposures, which cause mutations, deplete vitamin D3 in the skin.

*LIFE STYLE including smoking*

Life style – outdoor/indoor life, smoking etc can influence the risk to melanoma. Smokers have lower plasma antioxidant levels than non-smokers and this leads to decreased protective efficacy of the antioxidant defense system.

**CANCER SUSCEPTIBILITY**

*FAMILY HISTORY (GENOTYPE)*

Approximately 10% of melanoma is inherited (Familial). About 40 percent of familial melanoma is associated with chromosome 9p. There are geographical variations in the melanoma susceptibility genes CDKN2A and CDK4.

*DNA POLYMORPHISMS/ SOMATIC MUTATIONS*

The oncogenic mutations in the B-RAF and N-RAS genes constitute the initiating somatic events followed by loss of a major check point gene mainly CDKN2A or in some cases p53 or PTEN, which is connected with high risk of melanoma. Some of the genetic variants in the DNA repair gene XRCC1 have also been associated with melanoma.

*DNA REPAIR CAPACITY*

There are substantial individual differences in DNA repair capacity depending on nutritional and health status of the individuals or on polymorphisms in repair genes.

*ANTIOXIDANT CAPACITY*

Most melanoma cases are caused by free radicals induced indirect DNA damage, therefore it is important to efficiently scavenge or neutralize the reactive oxygen species.

MECHANISMS OF ACTION

*GENOME DAMAGE*

UVB can directly damage DNA causing apoptosis of keratinocytes by forming the sunburn cells. UVA causes indirect (oxidative) DNA damage through reactive oxygen radicals and is responsible for 92% of melanoma cases.

*BIOLOGICAL ACTIVITY*

UV light and ionising radiation, can induce DNA damage. Cascade of genetic and epigenetic cganges can interfere with biological processes in cells and thus influence cell cycle and progression of cells.

## Questions

**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to UV and radiation on melanoma cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
|---|---|---|---|---|
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**What is your level of confidence in scientists' ability to predict the magnitude of the effect of individual susceptibility to UV on melanoma cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between UV and other exposure on melanoma cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**What is your level of confidence in scientists' ability to predict the impact of exposure to UV with the current knowledge of its mechanism of action on melanoma development?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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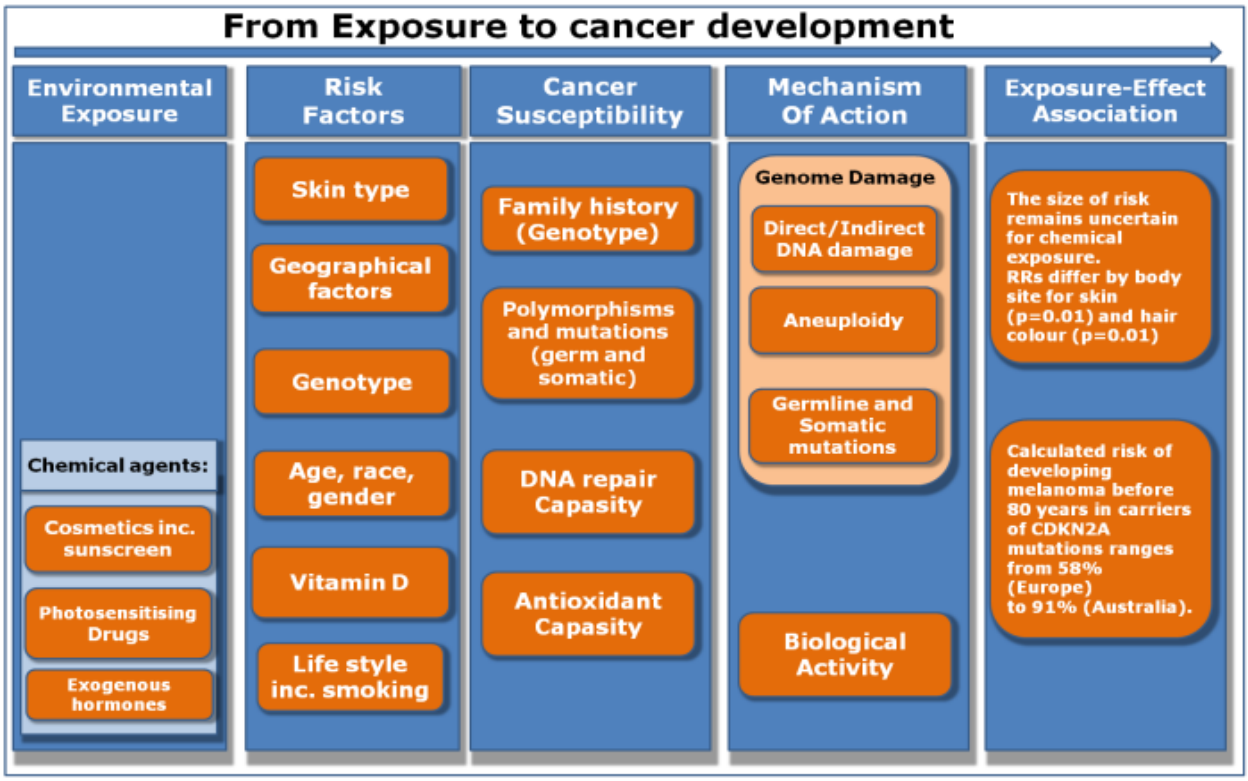
## Melanoma – Chemical agents




**RISK FACTORS**

*SKIN TYPE*

Malignant melanoma mainly afflicts people with white skin (Caucasian population). Risk of melanoma depends on skin type.

*GEOGRAPHICAL FACTORS*
Sun exposure plays a primary and supporting role in most melanoma tumors. Sunscreens are used more frequently in regions with higher UV radiation.

*GENOTYPE*
Approximately 10% of melanoma is inherited (Familial). Mutations are found in the genes CDKN2A and CDK4.

*RACE, GENDER AND AGE*
Malignant melanoma mainly afflicts Caucasian population. Among cases aged 15-30 years, females have a higher risk, after age 30, incidence is higher among males.

*VITAMIN D*
Indoor solar UVA exposures, which cause mutations, depletes vitamin D3 in the skin.

*LIFE STYLE INC. SMOKING*
Life style – outdoor/indoor life, smoking etc can influence the risk to melanoma. Smokers have lower plasma antioxidant levels than non-smokers and this leads to decreased protective efficacy of the antioxidant defense system. Although sunscreens prevent sunburn, there is still missing epidemiological or laboratory evidence of protective or risk effect to melanoma.

**CANCER SUSCEPTIBILITY**
*FAMILY HISTORY (GENOTYPE)*
Approximately 10% of melanoma is inherited (Familial). About 40 percent of familial melanoma is associated with chromosome 9p. There are geographical variations in the melanoma susceptibility genes CDKN2A and CDK4.

*DNA POLYMORPHISMS/ SOMATIC MUTATIONS*
The oncogenic mutations in the B-RAF and N-RAS genes constitute the initiating somatic events followed by loss of a major check point gene mainly CDKN2A or in some cases p53 or PTEN, which is connected with high risk of melanoma. Some of the genetic variants in the DNA repair gene XRCC1 have also been associated with melanoma.

*DNA REPAIR CAPACITY*
There are substantial individual differences in DNA repair capacity depending on nutritional and health status of the individuals or on polymorphisms in repair genes.

*ANTIOXIDANT CAPACITY*
Most melanoma cases are caused by free radicals induced indirect DNA damage, therefore it is important to efficiently scavenge or neutralize the reactive oxygen species.

**MECHANISMS OF ACTION**
*GENOME DAMAGE*
Chemical exposure can damage DNA or directly and indirectly induce genomic changes.

*BIOLOGICAL ACTIVITY*
Chemical exposure can induce directly and indirectly DNA damage, oxidative damage or influence gene expression. Cascade of genetic and epigenetic cganges can interfere with biological processes in cells and thus influence cell cycle and progression of cells.

## Questions

**What is your level of confidence in scientists' ability to predict the impact of environmental exposure to cosmetics including sunscreen on melanoma cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**What is your level of confidence in scientists' ability to predict the magnitude of the effect of individual susceptibility to cosmetics including sunscreen on melanoma cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between cosmetics incl. sunscreen and other exposure on melanoma cancer risk?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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**What is your level of confidence in scientists' ability to predict the impact of exposure to cosmetics incl. sunscreen with the current knowledge of its mechanism of action on melanoma development?**

| Very high confidence. At least 9 in 10 chance of being correct | High confidence. At least 7 in 10 chance of being correct. | Medium confidence. At least 5 in 10 chance of being correct. | Low confidence. At least 3 in 10 chance of being correct. | Very low confidence. Less than 2 out of 10 chance of being correct. |
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TITLE

HENVINET

Evaluation questionnaire – Causal chain for cancer

PROJECT LEADER

Alena Bartonova

NILU PROJECT NO.

U-106169

AUTHOR(S)

Aileen Yang[1)] and Alena Bartonova[1)], Editors

Authors:
Aleksandra Fucic[2)] and Domenico Franco Merlo[3)]

[1)] Norwegian Institute for Air Research, Kjeller, Norway
[2)] Institute for Medical Research and Occupational Health, Zagreb, Croatia
[3)] National Cancer Research Institute, Epidemiology and Biostatistics & Clinical Trials and Bioethics, Genoa, Italy

CLASSIFICATION *

A

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| KEYWORDS | | |
|---|---|---|
| Brain cancer, Breast tumors, Colorectal tumors | Leukemia, Lung mesothelioma, melanoma | Knowledge evaluation, Cause-effect diagram |

ABSTRACT

The HENVINET consortium has developed a questionnaire to identify knowledge gaps in the state of the art in scientific knowledge. Literature reviews covered all elements that compose the causal chain of the different environmental health issues from emissions to exposures, to effects and to health impacts. Ultimately, the aim is to discuss the implications of these for policy and research.

In this evaluation we focus on various aspects of the cause-effect relationship between our living environment and increased risk of cancer development. Occupational exposure to carcinogens is not included. Six cancer types are considered; brain cancer, breast tumors, colorectal tumors, leukemia, lung mesothelioma and melanoma.

** Classification*
*A Unclassified (can be ordered from NILU)*
*B Restricted distribution*
*C Classified (not to be distributed)*

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