Understanding the development of cancer for pesticide applicators and handlers

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Board of Pesticides Control

Maine Department Agriculture, Conservation, & Forestry

Why talk about cancer?

- Cancer is not the only concern with pesticide exposure!

- I've been asked to speak about glyphosate recently
  - ➢Highlighted some basic misunderstandings about cancer

- Also, …

Why talk about cancer?

... because it affects nearly everybody either directly or indirectly

38.4%

Of all men and women in the US will receive a cancer diagnosis at some point in their lives.

In the US, the lifetime risk of developing cancer is
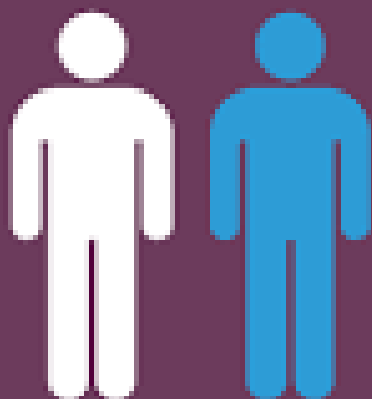
1 in 2 men & 1 in 3 women

Source: American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2006.

1991 ⟶ 2015

THE OVERALL CANCER DEATH RATE IN THE UNITED STATES **FELL**

↓ **26%**

SEER Cancer Statistics Review, 1975–2015
cancer.gov

Note: this is death rate not incidence rate.

1991 → 2015

THE OVERALL CANCER DEATH RATE IN THE UNITED STATES FELL 26%

SEER Cancer Statistics Review, 1975–2015
cancer.gov

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NIH's cancer-causing chemicals in the environment:

- Aflatoxins
- Aristolochic Acids
- Arsenic
- Asbestos
- Benzene
- Benzidine
- Beryllium
- 1,3-Butadiene
- Cadmium
- Coal Tar and Coal-Tar Pitch
- Coke-Oven Emissions
- Crystalline Silica (respirable size)
- Erionite
- Ethylene Oxide
- Formaldehyde
- Hexavalent Chromium Compounds
- Indoor Emissions from the Household Combustion of Coal
- Mineral Oils: Untreated and Mildly Treated
- Nickel Compounds
- Radon
- Secondhand Tobacco Smoke (Environmental Tobacco Smoke)
- Soot
- Strong Inorganic Acid Mists Containing Sulfuric Acid
- Thorium
- Trichloroethylene
- Vinyl Chloride
- Wood Dust

- Constantly exposed to carcinogens in our ideal diet
  - Estimated we consume 1.5 grams of pesticide daily
  - These are naturally occurring plant protectants
  - Only a few (< 100) tested but ~50% of them are mutagens

- Begs the question:
  if we eat this many cancer causing foods,
  how do we not all die of cancer?

- Reality is that our body is full of mechanisms that prevent cancer.
- The development of a metastatic aggressive cancer is the result of failures at multiple levels throughout the development of cancer.
  - It takes many 'hits' to set cancer development in motion

- Reality is that our body is full of mechanisms that prevent cancer.
- The development of a metastatic aggressive cancer is the result of failures at multiple levels throughout the development of cancer.
    - It takes many 'hits' to set cancer development in motion

➢This is a reason why applicators are more at risk than the general population. Applicators have repeat exposures over long periods of time.

Mutagens / Carcinogens

- Any substance which increase rate of mutation

- All mutagens are carcinogens.

- Examples are......
  - Radiations like X-ray, UV-ray, gamma ray
  - Chemicals like benzopyrenes, Aflatoxins
  - Hormones like estrogen

Tumors are what we typically think of when we think of cancer.
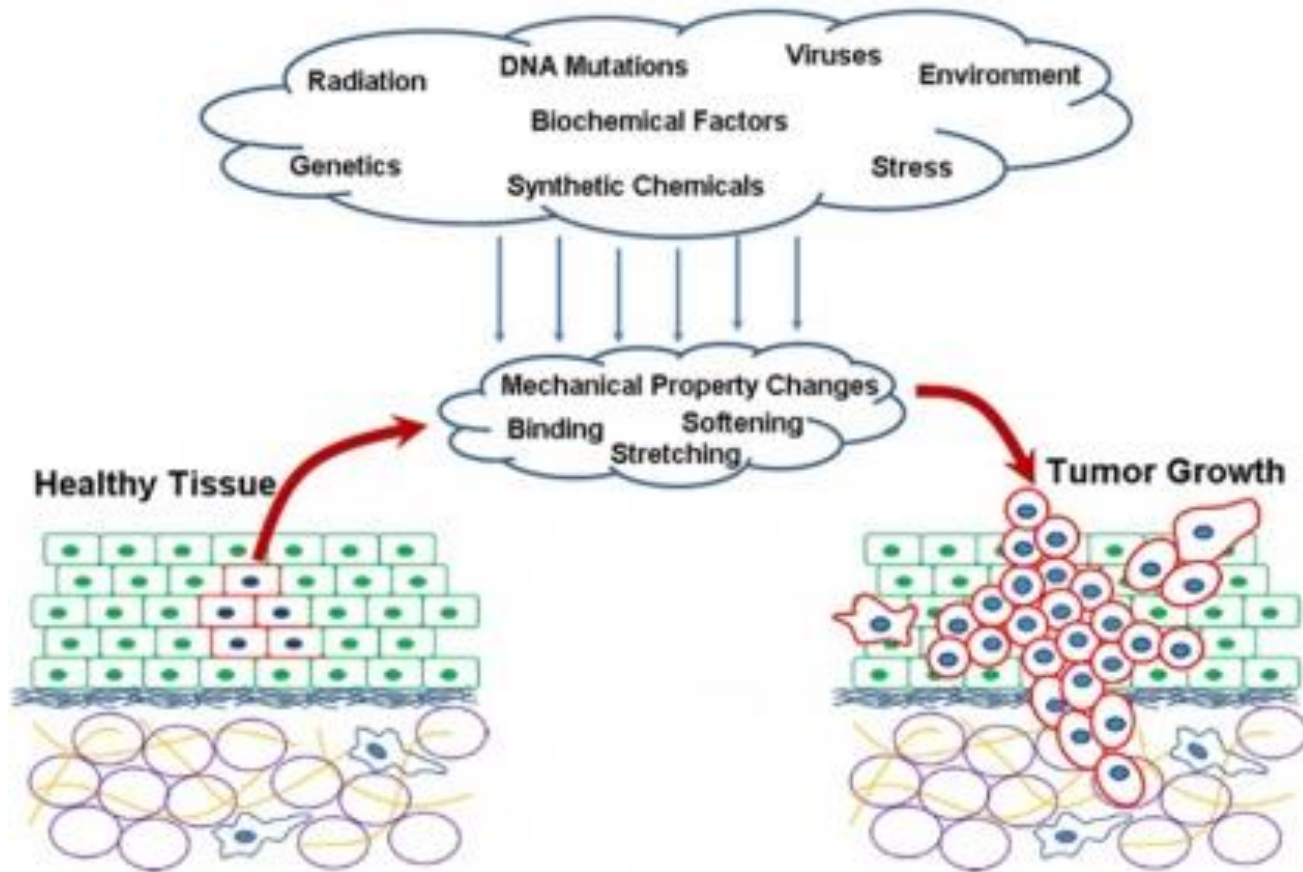
Normal: regulated cell growth

Cancer: uncontrolled cell growth

So, on to the details

Interphase

G_1/S checkpoint

S
DNA replicates

G_1
growth

G_2
growth, preparation for cell division

G_2/S checkpoint

Cytokinesis

Mitosis

M checkpoint

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https://radiationtherapycompany.weebly.com/biochemical-pathway.html
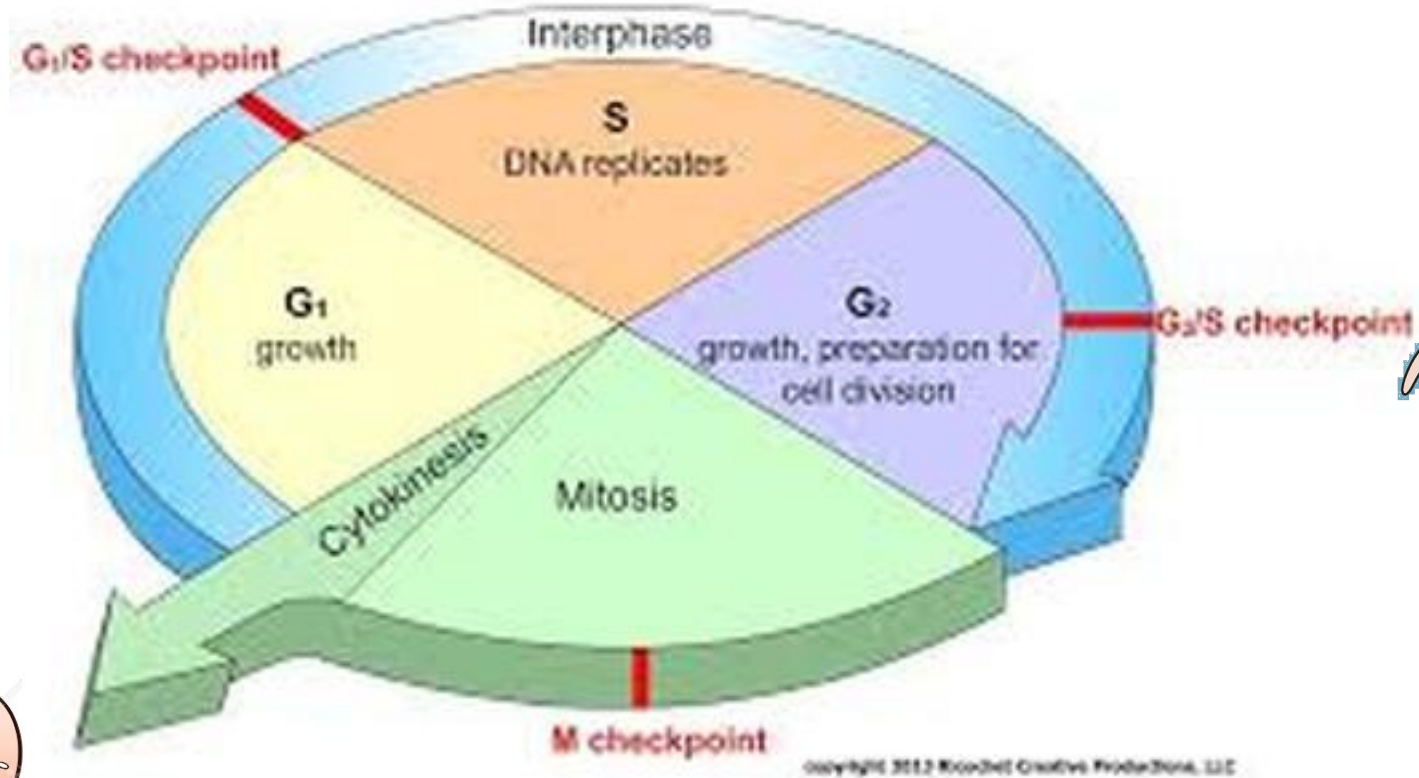
Loss of Normal Growth Control

Normal cell division

Cell damage— no repair

Cell Suicide or Apoptosis

First mutation

Second mutation

Third mutation

Fourth mutation

Malignant cells tumor growth
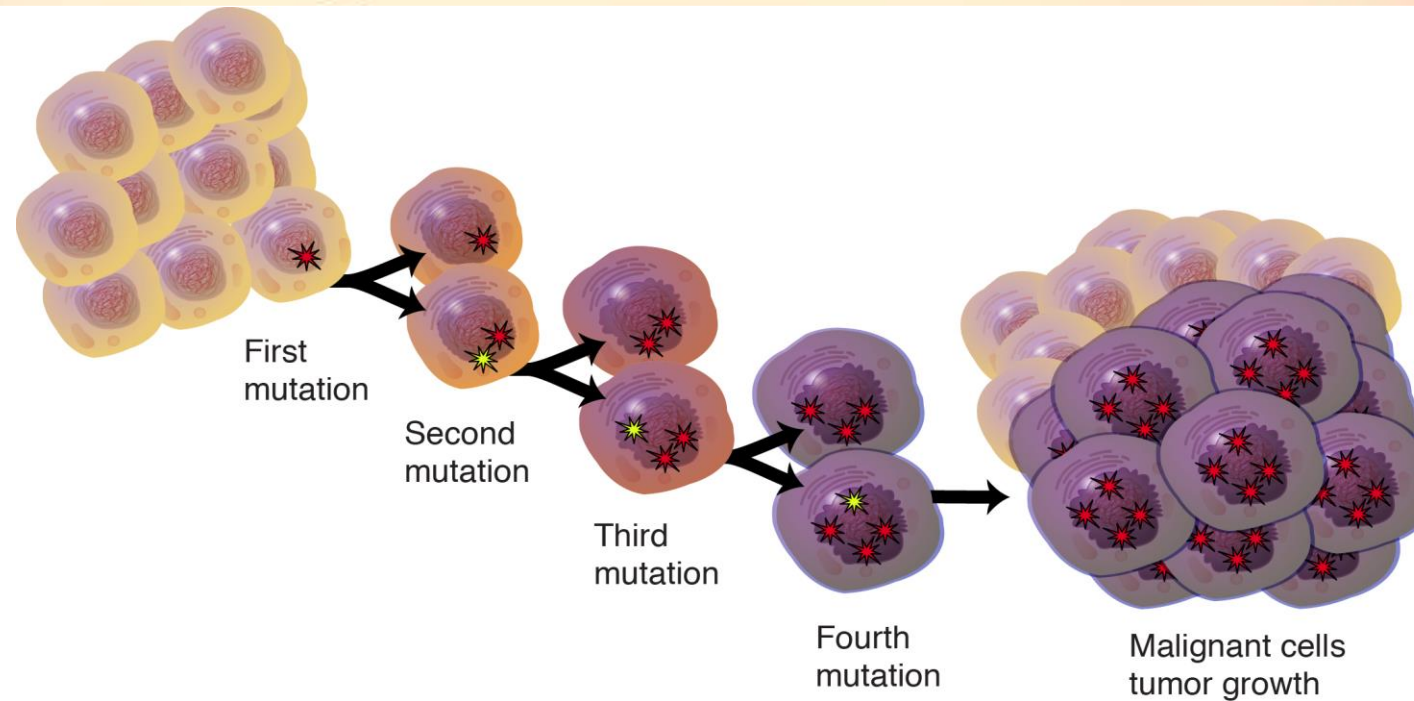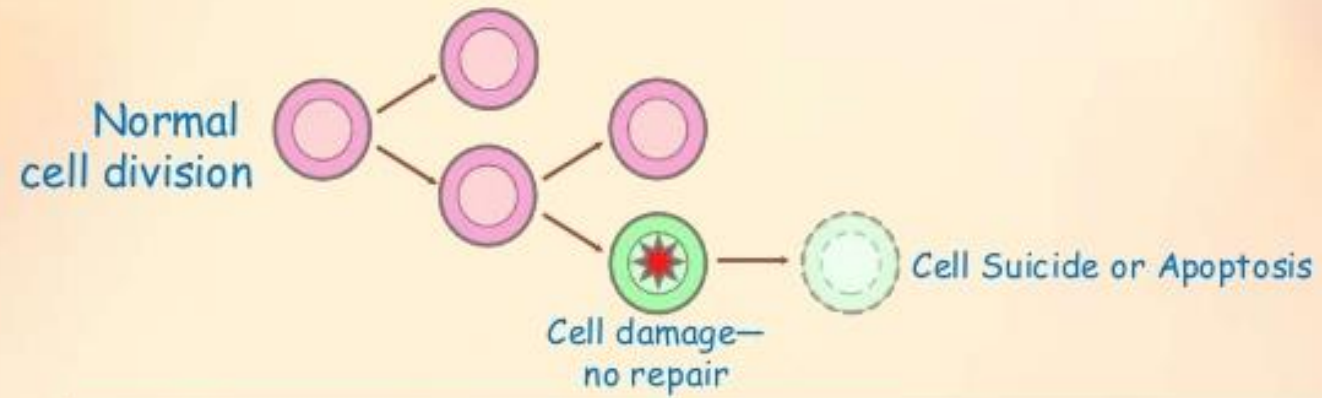
Stages of cancer development

- Stage 0 means there's no cancer, only abnormal cells with the potential to become cancer.

- Stage I means the cancer is small and only in one area. This is also called early-stage cancer.

- Stage II and III mean the cancer is larger and has grown into nearby tissues or lymph nodes.

- Stage IV means the cancer has spread to other parts of your body. It's also called advanced or metastatic cancer.

Stages of cancer development
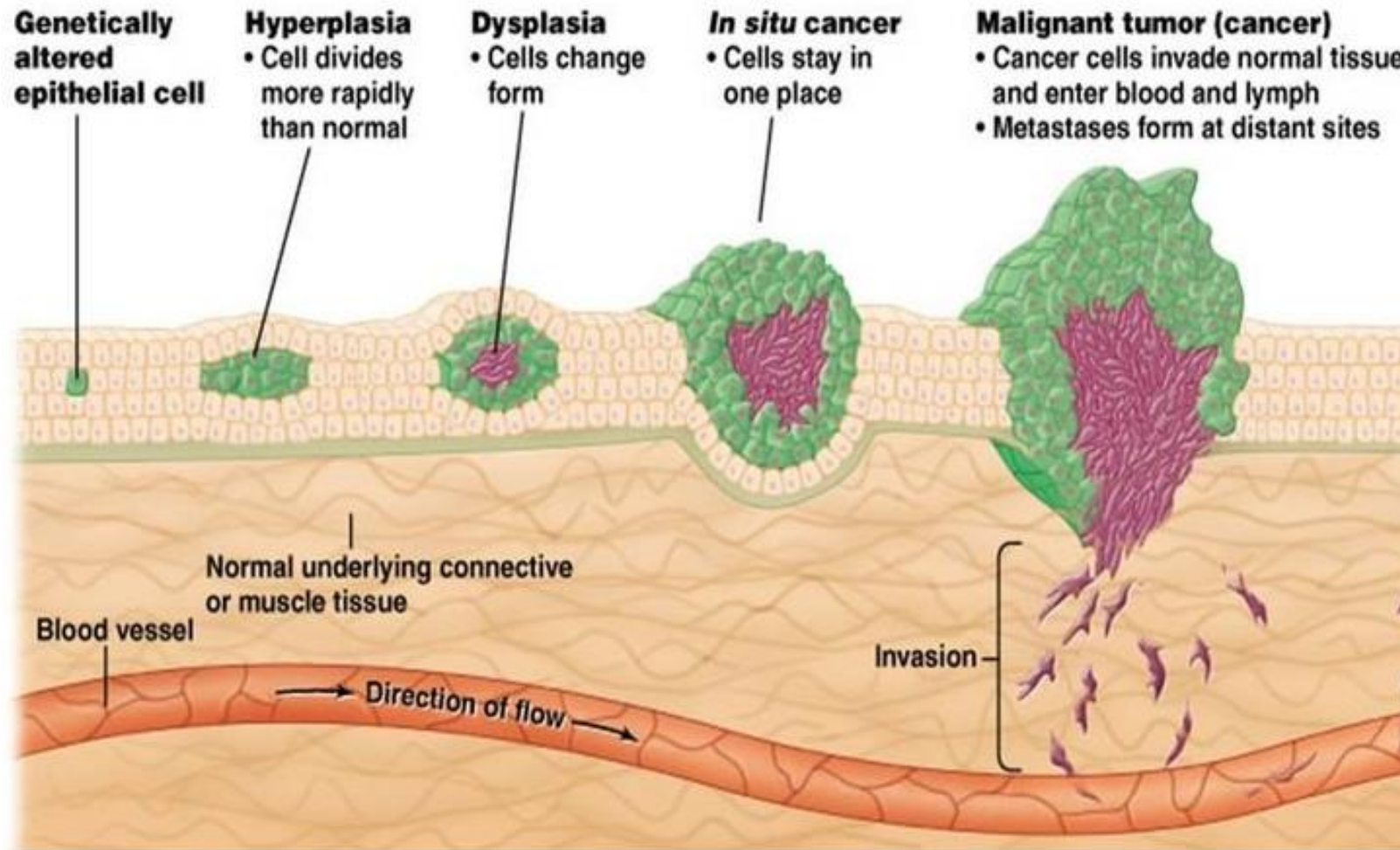
Etiology of Cancer

- Genetic factors
- hormonal
- Racial & geographic factors
- Environmental factors
- Chemical factors
- Age
- Sex

Genes involved with cancer

- Oncogenes: genes that promote cancer
- Proto-oncogenes: normal gene before mutations
- Tumor suppressor genes: genes that normally restrain cell growth but can break
- Mutator /DNA repair genes: normally fix broken DNA but can break
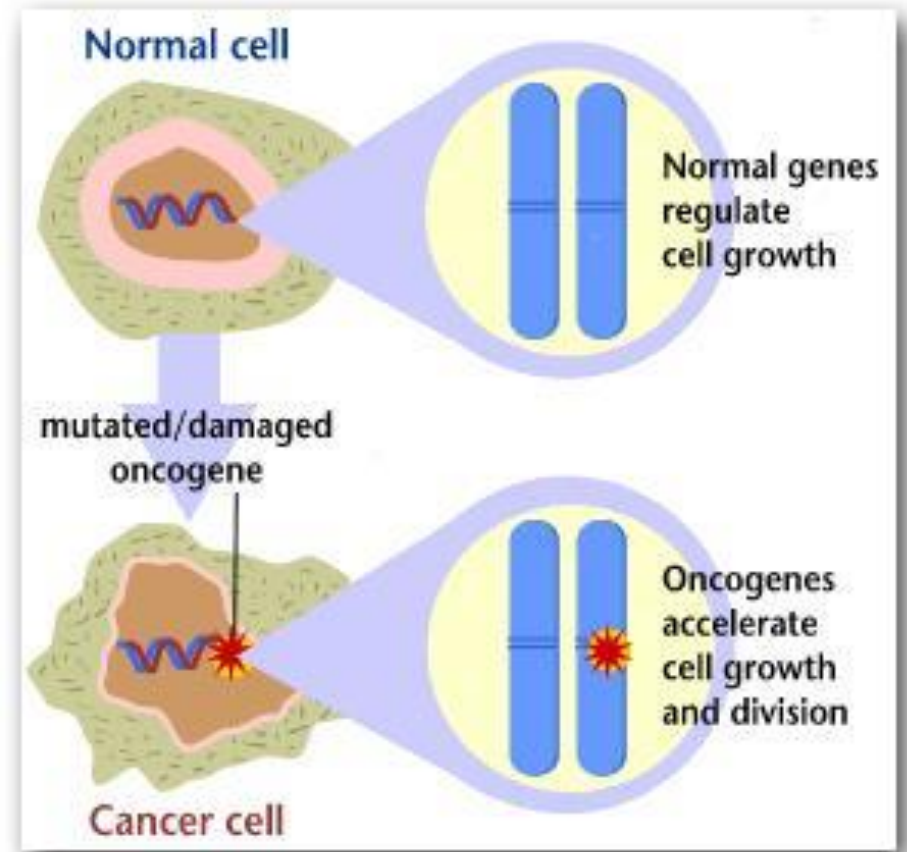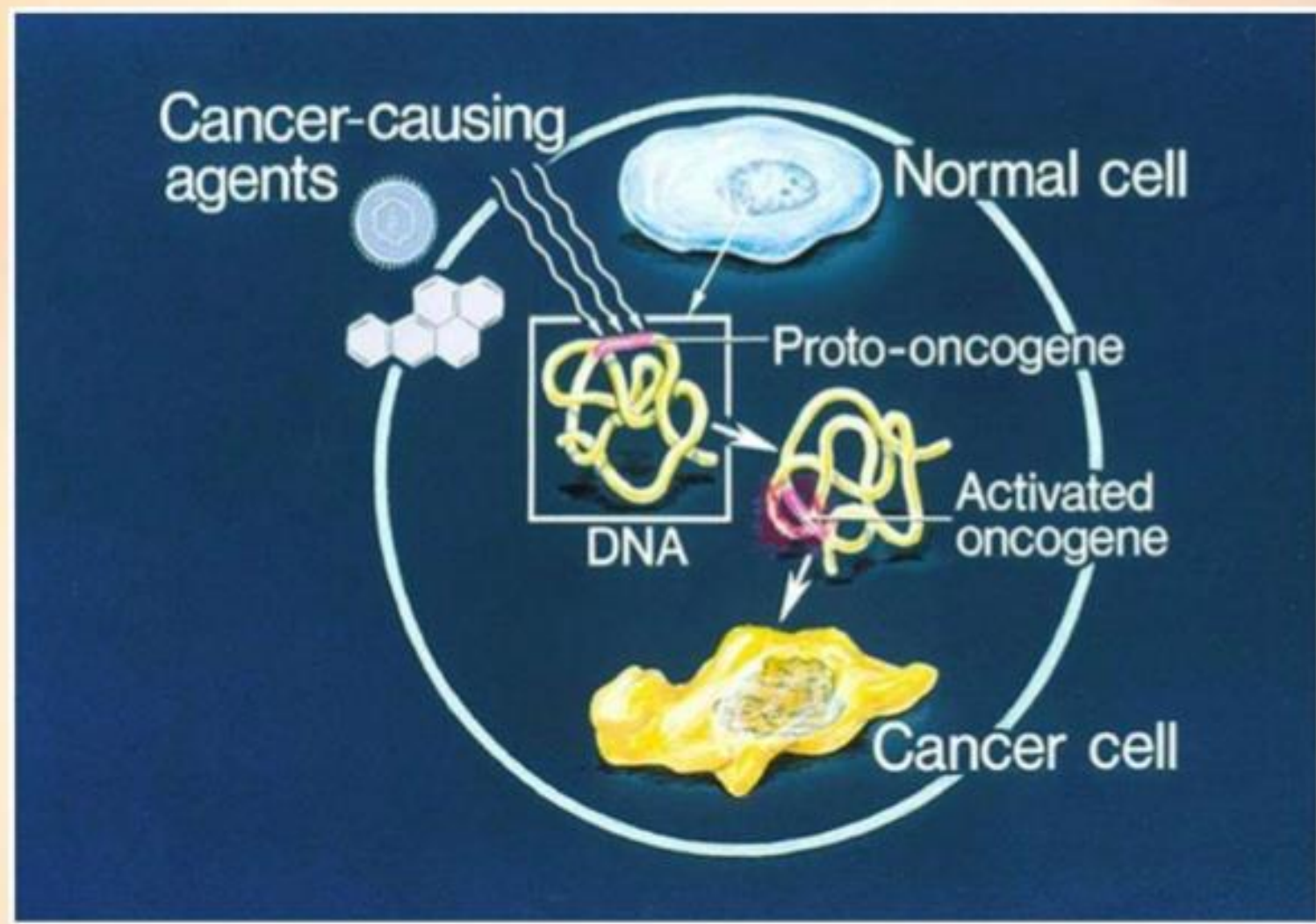
Mutations in Tumor Suppressor Genes

Normal genes (regulate cell growth) — Tumor suppressor genes — CANCER

1st mutation (susceptible carrier) — Tumor suppressor genes — Active oncogene — CANCER

2nd mutation or loss (leads to cancer) — No brakes! — CANCER

No brakes! — Active oncogene — CANCER

National Cancer Institute
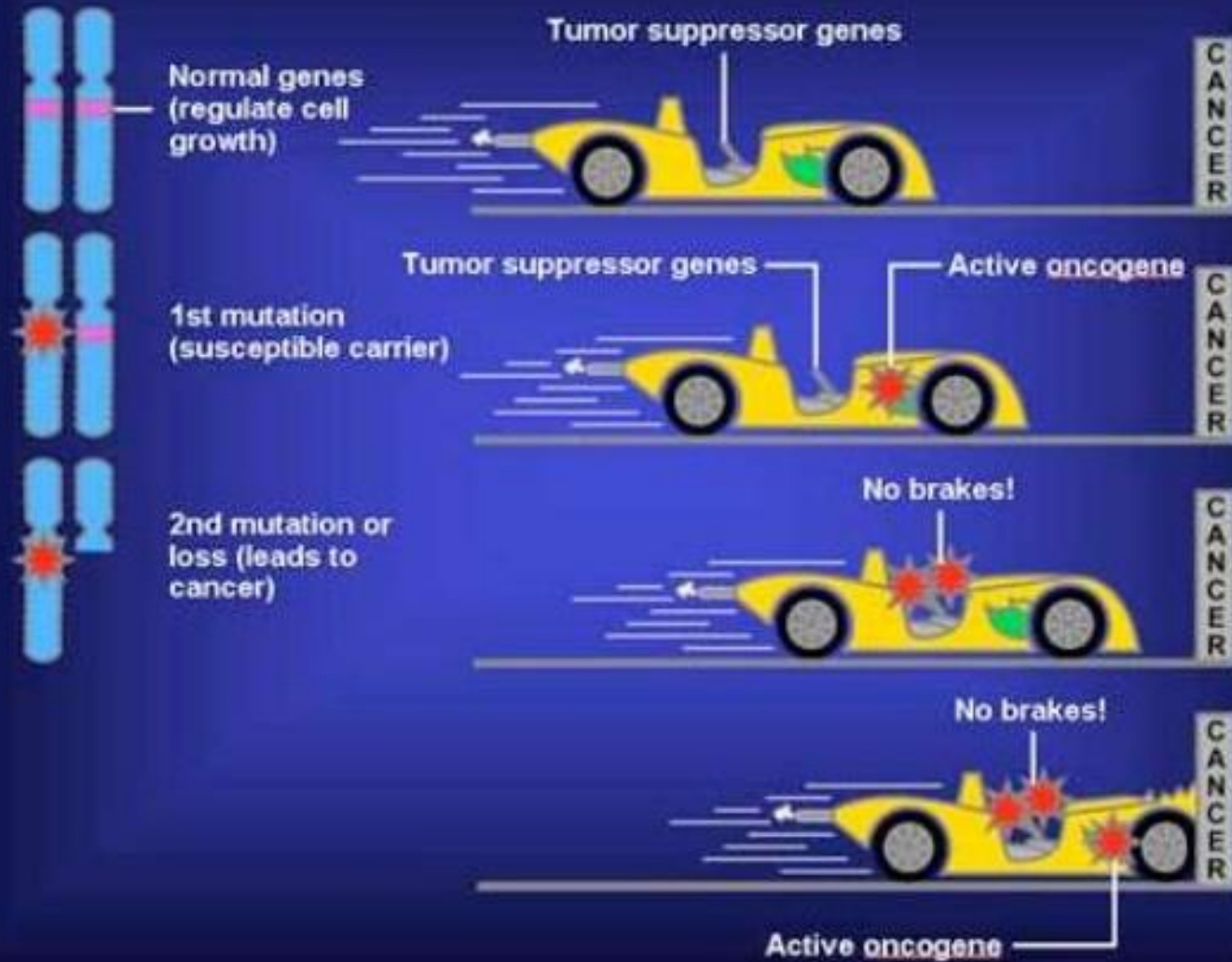
Viruses and Cancer

- Viruses promoting human cancer. These include both **DNA viruses** and **retroviruses**, type of RNA viruses.

Tumor Viruses

Virus	Type of Cancer
Epstein-Barr virus	Burkitt's lymphoma
Human papillomavirus	Cervical cancer
Hepatitis B virus	Liver cancer
Human T-cell lymphotrophic virus	Adult T-cell leukemia
Kaposi's sarcoma-associated herpesvirus	Kaposi's sarcoma

Tobacco Use and Cancer
Some Cancer-Causing Chemicals in Tobacco Smoke

aminostilbene
arsenic
benz[a]anthracene
benz[a]pyrene
benzene
benzo[b]fluoranthene
benzo[c]phenanthrene
benzo[j]fluoranthene
cadmium
chrysene
dibenz[a,c]anthracene
dibenzo[a,e]fluoranthene
dibenz[a,h]acridine
dibenz[a,j]acridine
dibenzo[c,g]carbazole
N-dibutylnitrosamine
2,3-dimethylchrysene

indeno[1,2,3-c,d]pyrene
5-methylchrysene
3-methylfluoranthene
alpha-naphthylamine
nickel compounds
N-nitrosodimethylamine

N-nitrosomethylethylamine
N-nitrosodiethylamine
N-nitrosonornicotine
N-nitrosoanabasine
N-nitrosopiperidine
polonium-210

DNA Structure

5' - end 3' - end

Hydrogen bonds

Complementary
nitrogenous bases

Sugar - phosphete
backbones

DNA double helix

5' 3'

1 spiral coil - 3,4 nm
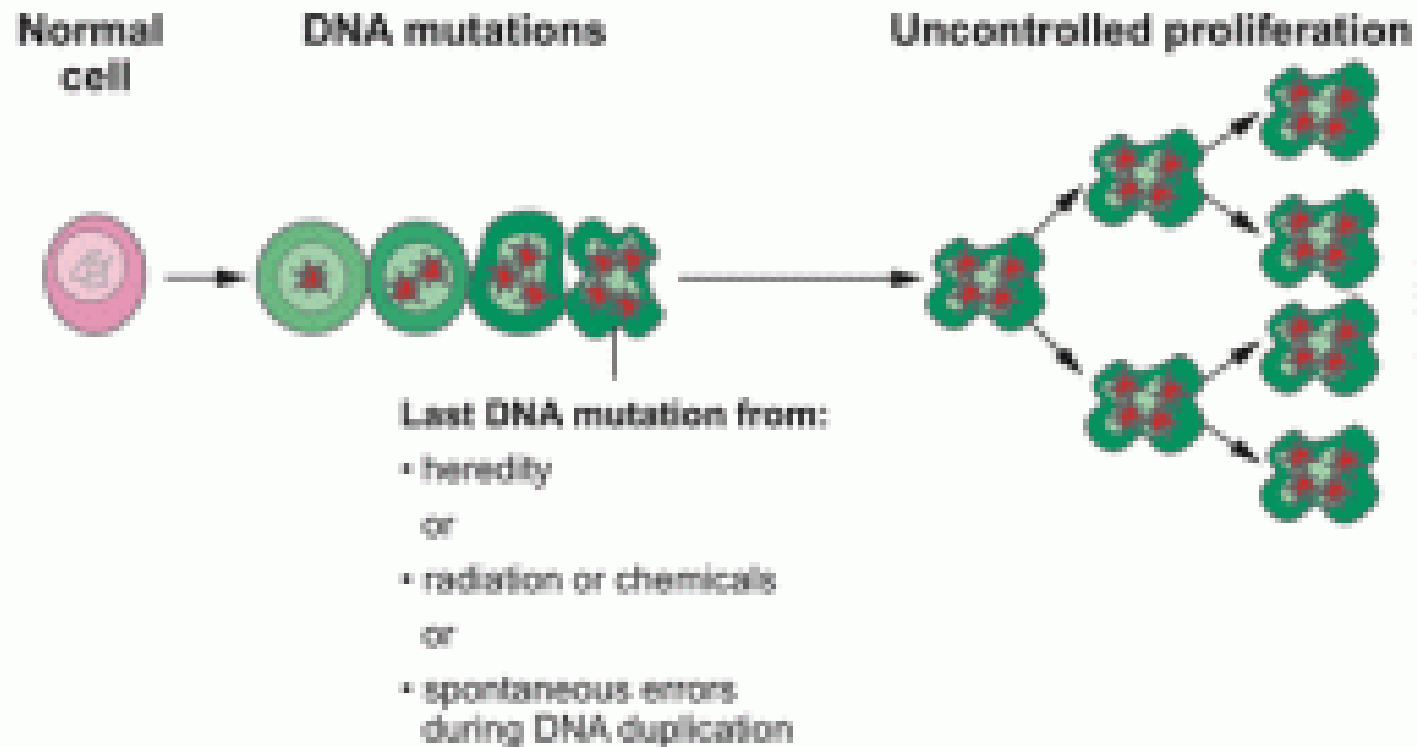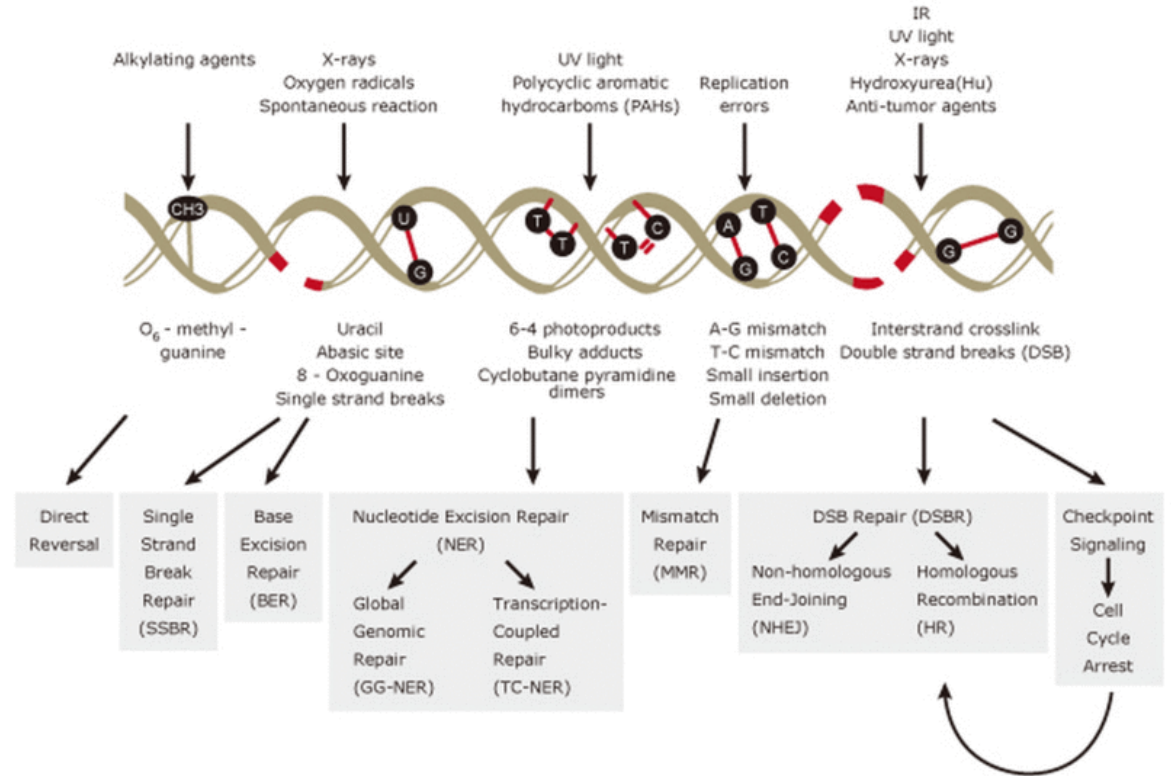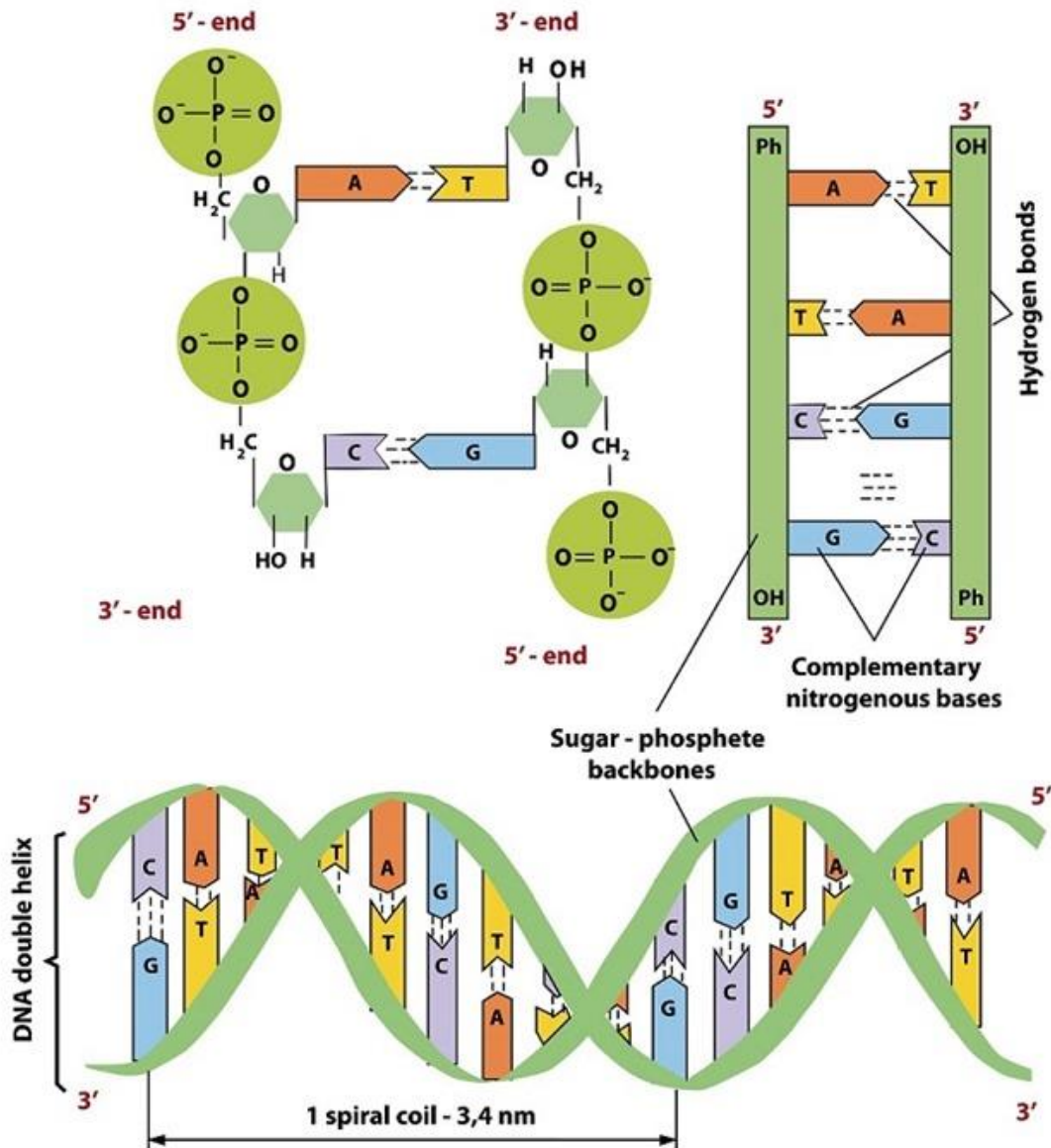
Adenine (A) Thymine (T) Guanine (G) Cytosine (C)

Alkylating agents | X-rays | UV light | Replication | IR
 | Oxygen radicals | Polycyclic aromatic | errors | UV light
 | Spontaneous reaction | hydrocarboms (PAHs) | | X-rays
 | | | | Hydroxyurea(Hu)
 | | | | Anti-tumor agents

O₆ - methyl -
guanine

Uracil
Abasic site
8 - Oxoguanine
Single strand breaks

6-4 photoproducts
Bulky adducts
Cyclobutane pyramidine
dimers

A-G mismatch
T-C mismatch
Small insertion
Small deletion

Interstrand crosslink
Double strand breaks (DSB)

Direct
Reversal

Single
Strand
Break
Repair
(SSBR)

Base
Excision
Repair
(BER)

Nucleotide Excision Repair
(NER)

Global
Genomic
Repair
(GG-NER)

Transcription-
Coupled
Repair
(TC-NER)

Mismatch
Repair
(MMR)

DSB Repair (DSBR)

Non-homologous
End-Joining
(NHEJ)

Homologous
Recombination
(HR)

Checkpoint
Signaling

Cell
Cycle
Arrest

How does EPA classify carcinogenicity of pesticides?

- Carcinogenic to humans.
- Likely to be carcinogenic to humans.
- Suggestive evidence of carcinogenic potential.
- Inadequate information to assess carcinogenic potential.
- Not likely to be carcinogenic to humans.
- Multiple descriptors (differing routes).

(2005)

In our daily lives what causes cancer?

In our daily lives what causes cancer?

- I'm warning you this answer is really boring.

In our daily lives what causes cancer?

- I'm warning you this answer is really boring.

       ----> Do the things your mother told you to do.

For example: breast cancer

CANCER RESEARCH UK

How many **cancers** can be **prevented**?
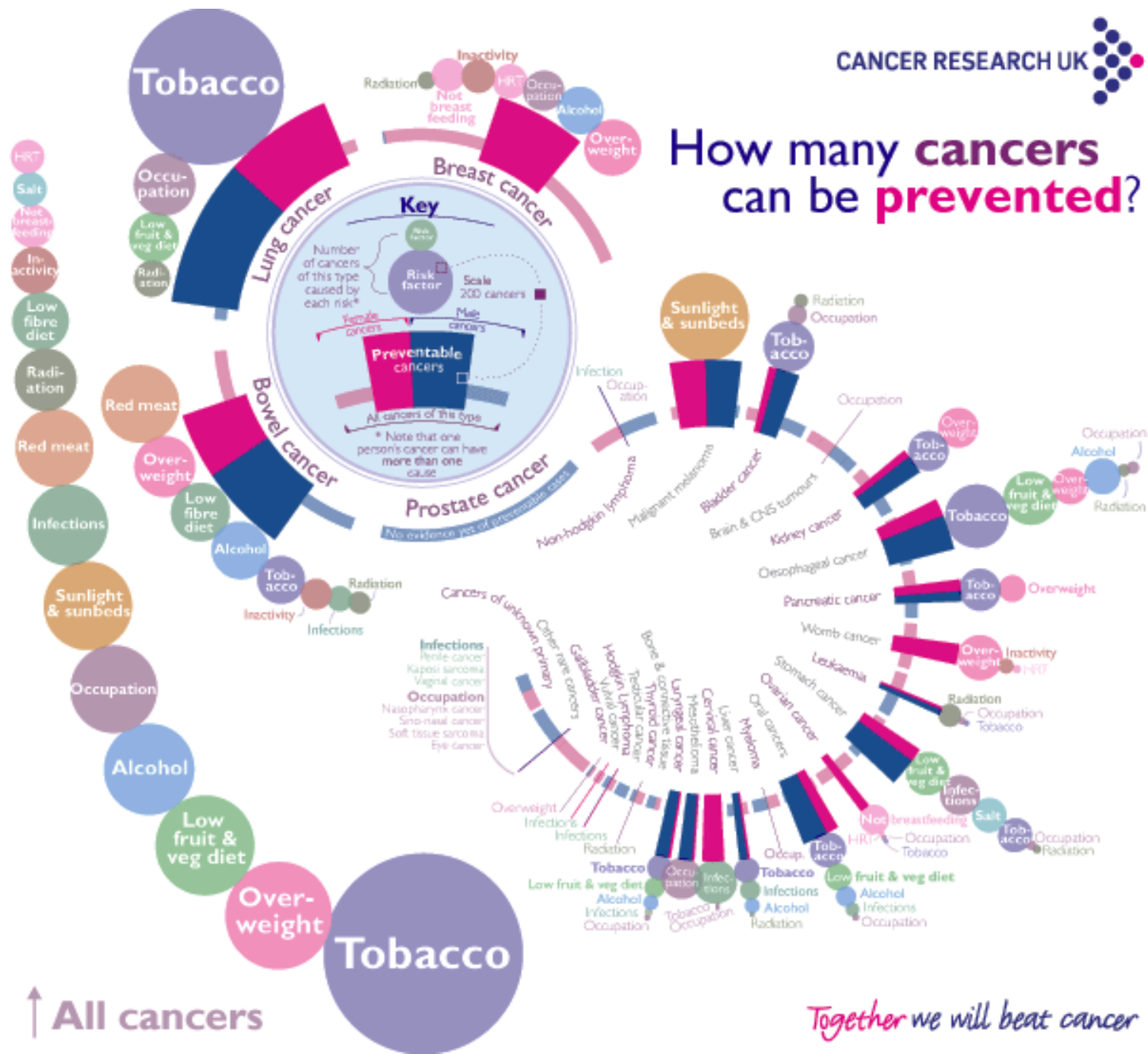
Together we will beat cancer

Key

Number of cancers of this type caused by each risk*

Risk factor

Scale 200 cancers

Female cancers | Male cancers

Preventable cancers

All cancers of this type

* Note that one person's cancer can have more than one cause

All cancers

Tobacco · Lung cancer · Breast cancer · Bowel cancer · Prostate cancer

Non-hodgkin lymphoma · Malignant melanoma · Bladder cancer · Brain & CNS tumours · Kidney cancer · Oesophageal cancer · Pancreatic cancer · Womb cancer · Leukaemia · Stomach cancer · Ovarian cancer · Oral cancers · Myeloma · Liver cancer · Cervical cancer · Mesothelioma · Laryngeal cancer · Bone & connective tissue · Thyroid cancer · Testicular cancer · Hodgkin Lymphoma · Gallbladder cancer · Other rare cancers · Cancers of unknown primary

Infections: Penile cancer, Kaposi sarcoma, Vaginal cancer

Occupation: Nasopharynx cancer, Sino-nasal cancer, Soft tissue sarcoma, Eye cancer

10 Leading Causes of Death by Age Group, United States – 2016

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
					Age Groups						
1	Congenital Anomalies 4,816	Unintentional Injury 1,261	Unintentional Injury 787	Unintentional Injury 847	Unintentional Injury 13,895	Unintentional Injury 23,984	Unintentional Injury 20,975	Malignant Neoplasms 41,291	Malignant Neoplasms 116,364	Heart Disease 507,118	Heart Disease 635,260
2	Short Gestation 3,927	Congenital Anomalies 433	Malignant Neoplasms 449	Suicide 436	Suicide 5,723	Suicide 7,366	Malignant Neoplasms 10,903	Heart Disease 34,027	Heart Disease 78,610	Malignant Neoplasms 422,927	Malignant Neoplasms 598,038
3	SIDS 1,500	Malignant Neoplasms 377	Congenital Anomalies 203	Malignant Neoplasms 431	Homicide 5,172	Homicide 5,376	Heart Disease 10,477	Unintentional Injury 23,377	Unintentional Injury 21,860	Chronic Low. Respiratory Disease 131,002	Unintentional Injury 161,374
4	Maternal Pregnancy Comp. 1,402	Homicide 339	Homicide 139	Homicide 147	Malignant Neoplasms 1,431	Malignant Neoplasms 3,791	Suicide 7,030	Suicide 8,437	Chronic Low. Respiratory Disease 17,810	Cerebro-vascular 121,630	Chronic Low. Respiratory Disease 154,596
5	Unintentional Injury 1,219	Heart Disease 118	Heart Disease 77	Congenital Anomalies 146	Heart Disease 949	Heart Disease 3,445	Homicide 3,369	Liver Disease 8,364	Diabetes Mellitus 14,251	Alzheimer's Disease 114,883	Cerebro-vascular 142,142
6	Placenta Cord. Membranes 841	Influenza & Pneumonia 103	Chronic Low. Respiratory Disease 68	Heart Disease 111	Congenital Anomalies 388	Liver Disease 925	Liver Disease 2,851	Diabetes Mellitus 6,267	Liver Disease 13,448	Diabetes Mellitus 56,452	Alzheimer's Disease 116,103
7	Bacterial Sepsis 583	Septicemia 70	Influenza & Pneumonia 48	Chronic Low Respiratory Disease 75	Diabetes Mellitus 211	Diabetes Mellitus 792	Diabetes Mellitus 2,049	Cerebro-vascular 5,353	Cerebro-vascular 12,310	Unintentional Injury 53,141	Diabetes Mellitus 80,058
8	Respiratory Distress 488	Perinatal Period 60	Septicemia 40	Cerebro-vascular 50	Chronic Low Respiratory Disease 206	Cerebro-vascular 575	Cerebro-vascular 1,851	Chronic Low. Respiratory Disease 4,307	Suicide 7,759	Influenza & Pneumonia 42,479	Influenza & Pneumonia 51,537
9	Circulatory System Disease 460	Cerebro-vascular 55	Cerebro-vascular 38	Influenza & Pneumonia 39	Influenza & Pneumonia 189	HIV 546	HIV 971	Septicemia 2,472	Septicemia 5,941	Nephritis 41,095	Nephritis 50,046
10	Neonatal Hemorrhage 398	Chronic Low Respiratory Disease 51	Benign Neoplasms 31	Septicemia 31	Complicated Pregnancy 184	Complicated Pregnancy 472	Septicemia 897	Homicide 2,152	Nephritis 5,650	Septicemia 30,405	Suicide 44,965

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

# 10 Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States – 2016

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Unintentional Suffocation 1,023	Unintentional Drowning 425	Unintentional MV Traffic 384	Unintentional MV Traffic 455	Unintentional MV Traffic 7,037	Unintentional Poisoning 14,631	Unintentional Poisoning 13,278	Unintentional Poisoning 13,439	Unintentional Poisoning 9,438	Unintentional Fall 29,668	Unintentional Poisoning 58,335
2	Homicide Unspecified 132	Unintentional MV Traffic 334	Unintentional Drowning 147	Suicide Suffocation 247	Unintentional Poisoning 4,997	Unintentional MV Traffic 7,010	Unintentional MV Traffic 5,075	Unintentional MV Traffic 5,536	Unintentional MV Traffic 5,397	Unintentional MV Traffic 7,429	Unintentional MV Traffic 38,748
3	Unintentional MV Traffic 88	Unintentional Suffocation 118	Unintentional Fire/Burn 78	Suicide Firearm 160	Homicide Firearm 4,553	Homicide Firearm 4,510	Suicide Firearm 3,099	Suicide Firearm 3,873	Suicide Firearm 4,067	Suicide Firearm 5,756	Unintentional Fall 34,673
4	Homicide Other Spec., Classifiable 63	Homicide Unspecified 114	Homicide Firearm 68	Unintentional Drowning 103	Suicide Firearm 2,683	Suicide Firearm 3,298	Homicide Firearm 2,555	Suicide Suffocation 2,112	Unintentional Fall 2,679	Unintentional Unspecified 5,021	Suicide Firearm 22,938
5	Undetermined Suffocation 60	Unintentional Fire/Burn 107	Unintentional Suffocation 35	Homicide Firearm 95	Suicide Suffocation 2,100	Suicide Suffocation 2,643	Suicide Suffocation 2,199	Suicide Poisoning 1,736	Suicide Poisoning 1,538	Unintentional Suffocation 3,631	Homicide Firearm 14,415
6	Undetermined Unspecified 38	Unintentional Pedestrian, Other 82	Unintentional Other Land Transport 24	Unintentional Other Land Transport 64	Unintentional Drowning 530	Undetermined Poisoning 855	Suicide Poisoning 1,144	Homicide Firearm 1,420	Suicide Suffocation 1,474	Unintentional Poisoning 2,458	Suicide Suffocation 11,642
7	Unintentional Drowning 38	Homicide Firearm 64	Unintentional Pedestrian, Other 18	Unintentional Fire/Burn 52	Suicide Poisoning 426	Suicide Poisoning 767	Undetermined Poisoning 788	Unintentional Fall 1,238	Unintentional Suffocation 792	Adverse Effects 2,028	Suicide Poisoning 6,698
8	Homicide Suffocation 19	Homicide Other Spec., Classifiable 64	Unintentional Firearm 16	Unintentional Suffocation 39	Homicide Cut/Pierce 340	Unintentional Drowning 463	Unintentional Fall 515	Undetermined Poisoning 929	Homicide Firearm 738	Unintentional Fire/Burn 1,150	Unintentional Suffocation 6,610
9	Adverse Effects 18	Unintentional Firearm 34	Unintentional Struck by or Against 15	Unintentional Poisoning 28	Undetermined Poisoning 289	Homicide Cut/Pierce 420	Unintentional Drowning 396	Unintentional Drowning 478	Undetermined Poisoning 707	Suicide Poisoning 1,070	Unintentional Unspecified 6,507
10	Unintentional Natural/Environment 18	Unintentional Poisoning 34	Unintentional Other Transport 14	Unintentional Firearm 23	Unintentional Fall 199	Unintentional Fall 326	Homicide Cut/Pierce 350	Unintentional Suffocation 419	Unintentional Unspecified 625	Suicide Suffocation 859	Undetermined Poisoning 3,827

Centers for Disease Control and Prevention National Center for Injury Prevention and Control

Overdose Death Rates Involving Opioids, by Type, United States, 2000-2017
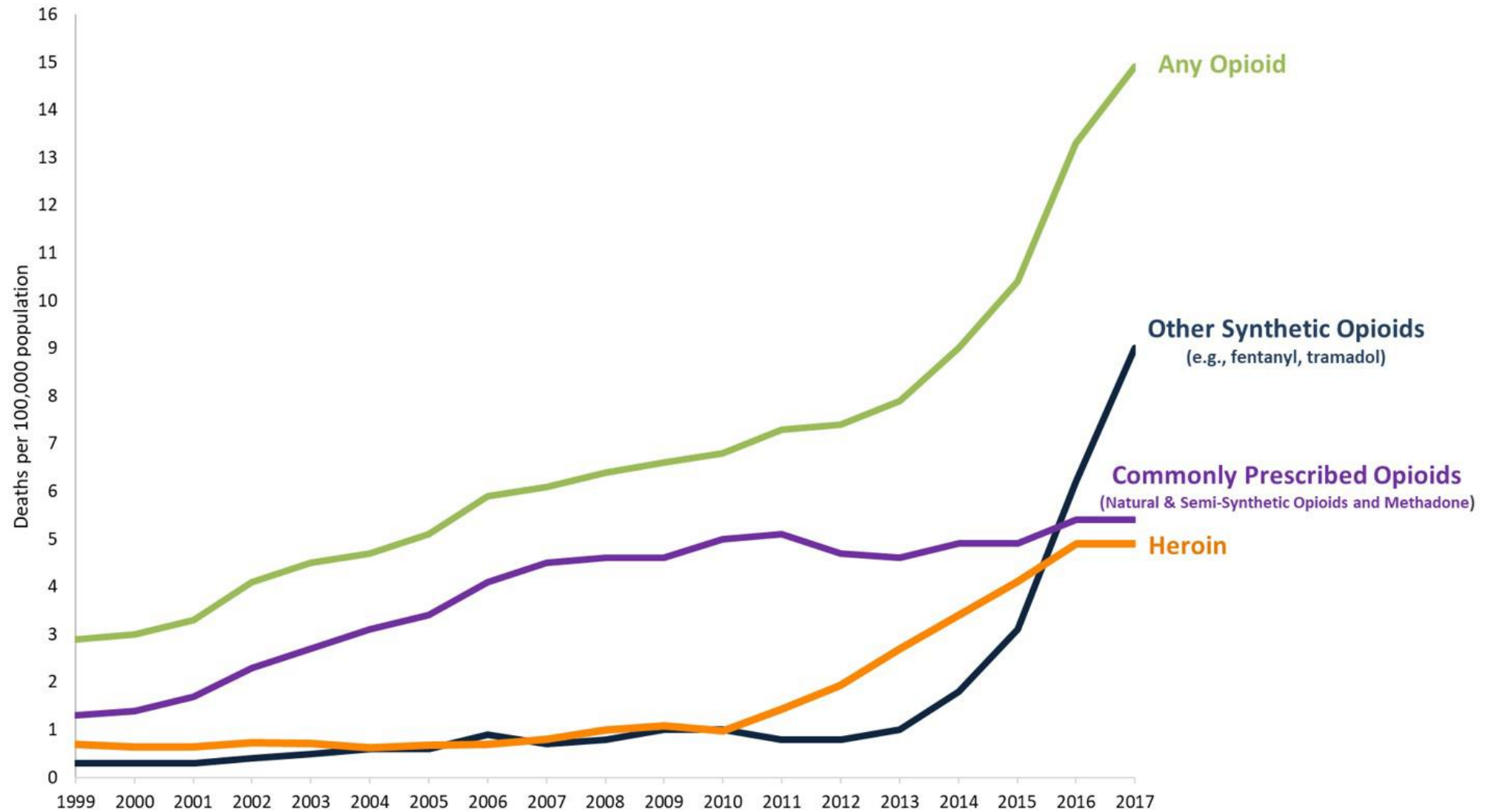
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://wonder.cdc.gov/.

"You mean pesticides and herbicides aren't the same?"

Please feel free to reach out to me at:

pamela.j.bryer@maine.gov

People also ask

Is Pesticide a carcinogen?	⌄
What is a carcinogen and list some examples?	⌄
What is a Group 3 carcinogen?	⌄
What can cause cancer list?	⌄

Feedback

Risk Assessment for Carcinogenic Effects | Air: Fate, Exposure ... - EPA
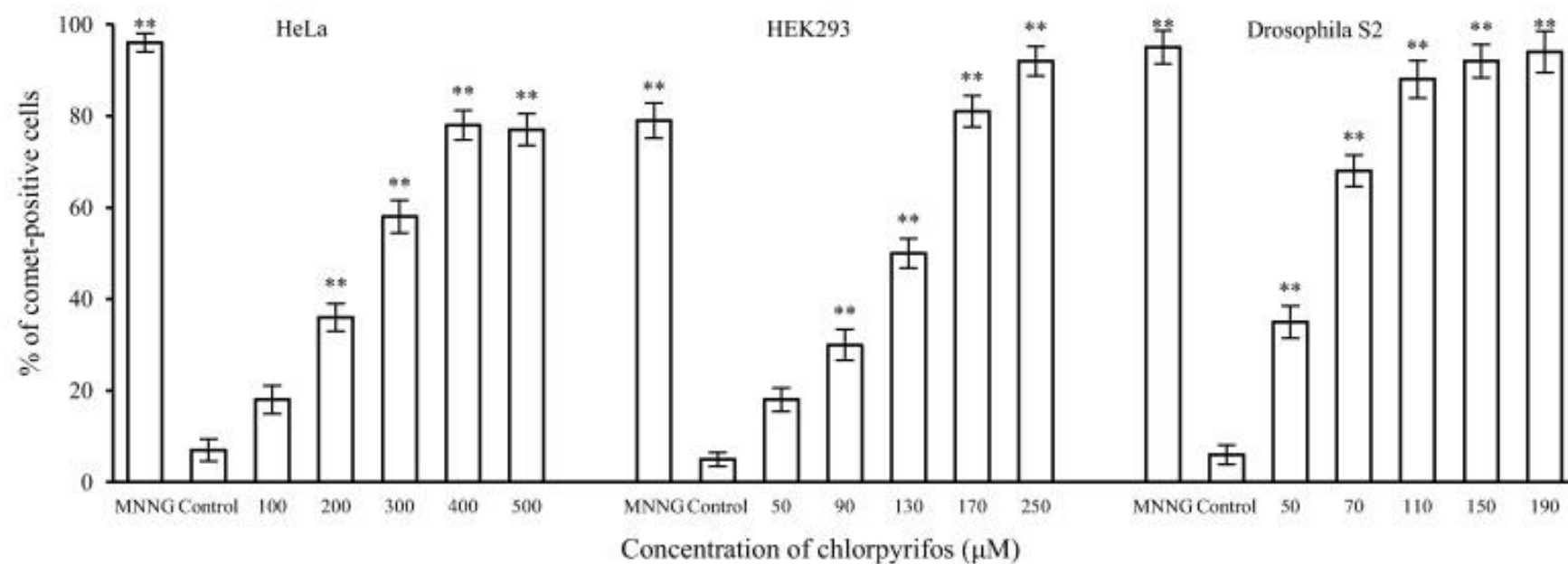https://www.epa.gov/fera/risk-assessment-carcinogenic-effects ▾
Jan 31, 2017 - **EPA** has since gained considerable experience in applying **cancer** risk assessment approaches. Concurrently, the science of risk assessment ...

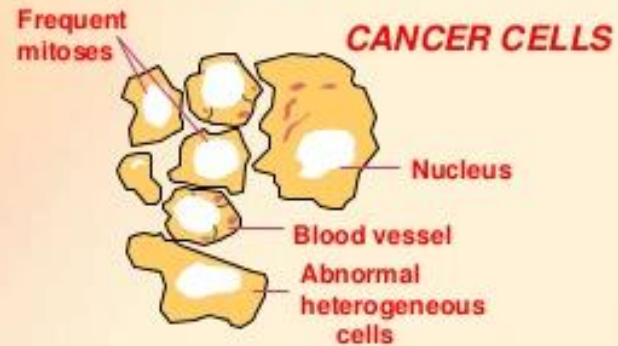### Evaluating Pesticides for Carcinogenic Potential | Pesticide ... - EPA
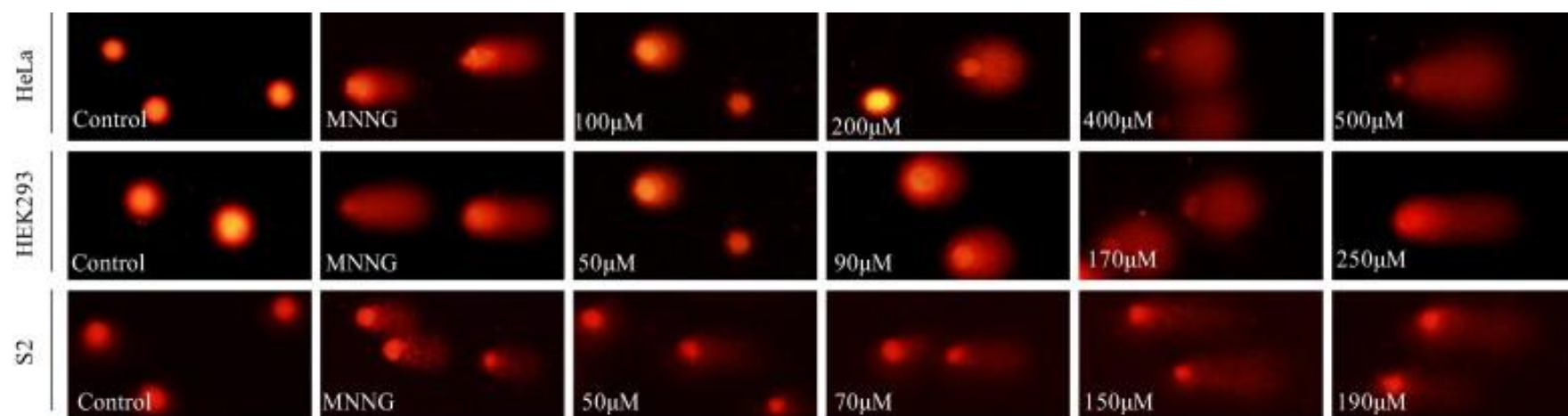
A

B

BIOCHEMICAL CHANGES IN CANCER CELLS AND NORMAL CELLS

CANCER CELLS

Frequent mitoses

Nucleus

Blood vessel

Abnormal heterogeneous cells

- Loss of **contact inhibition**
- Growing cells forms **multilayer**
- Increased Synthesis of **RNA & DNA**
- Decreased **catabolism of pyrimidine**
- ↑ **glycolysis** leads to **lactic acidosis**
- Synthesis of **fetal protein**
- Increase in **growth factor secretion**
- Increase in **oncogene expression**
- Loss of **tumor suppressor genes**

NORMAL CELLS

Normal cell

Few mitoses
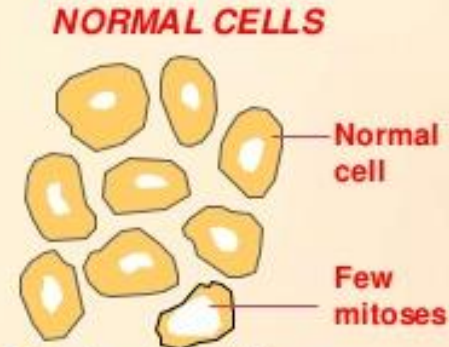
- Contact inhibition
- Forms **single layer**
- Synthesis of **RNA & DNA** is normal.
- **catabolism of pyrimidine** also normal
- Mostly **aerobic glycolysis**
- **Oncogene expression** is rare
- Intermittent or co-ordinated **growth factor secretion**
- **oncogene expression is absent**
- Presence of **tumor suppressor genes**

Pesticides

1. Premutagenic damages: DNA strand breaks, DNA adducts
2. Mutagenic damages (in base pairs)
3. Chromosomal aberrations

Micronucleus

Chromosomal break

Irregular number of homologous chromosomes

Sister chromatids exchange

DNA single strand break

Wrong Base

DNA double strand break

DNA adduct

Genetic damages
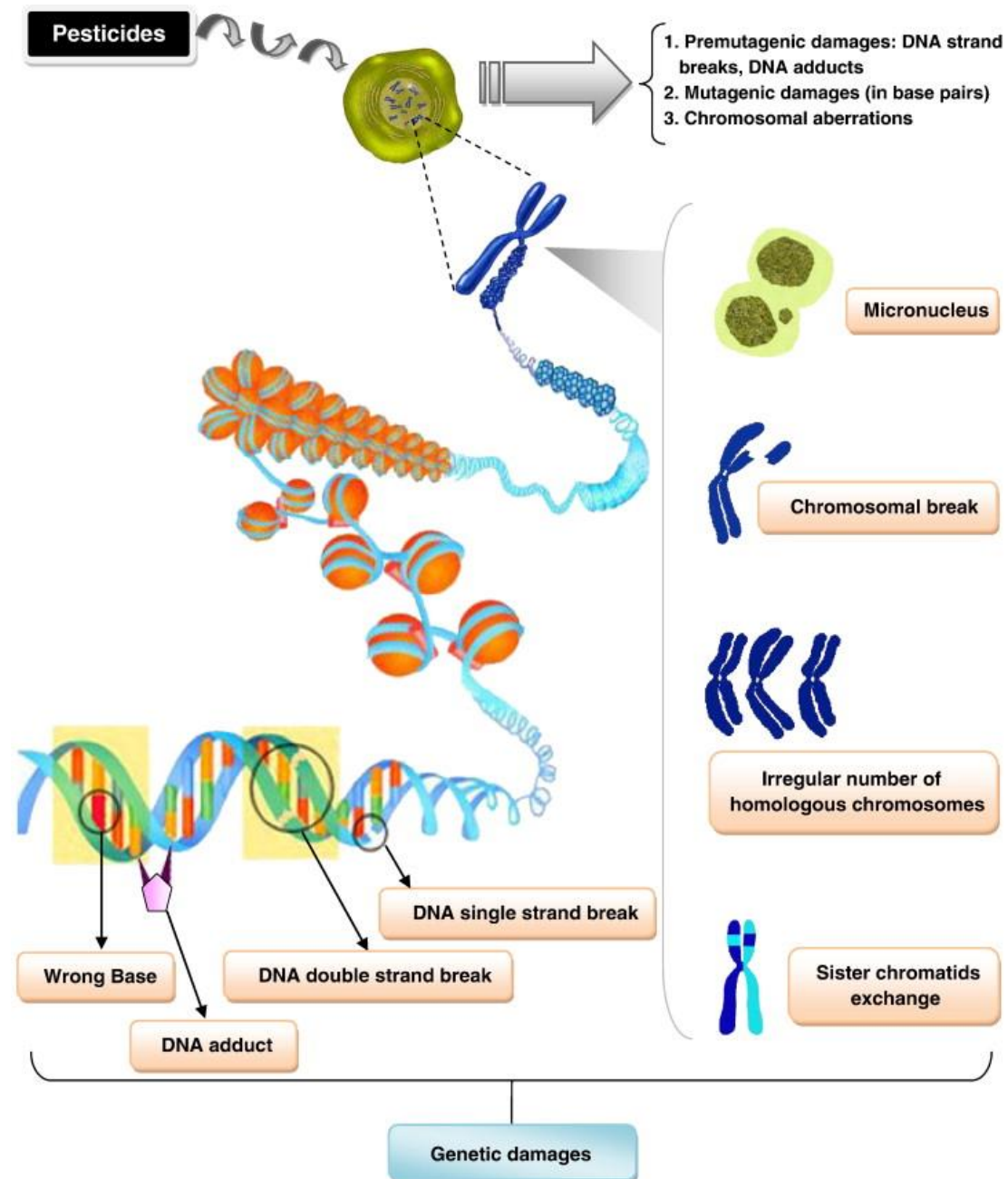
How does EPA classify carcinogenicity of pesticides?

Standard EPA classification categorization descriptions

Group A: "Human Carcinogen"

"This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer."

Group B (1 and 2): "Probable Human Carcinogen"

"This group includes agents for which the weight of evidence of human carcinogenicity based on epidemiologic studies is "limited" and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient". The group is divided into two subgroups. Usually, Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiological studies. It is reasonable, for practical purposes, to regard an agent for which there is "sufficient evidence of carcinogenicity " in animals as if it presented a carcinogenic risk to humans. Therefore, agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under Group B2."

Group C: "Possible Human Carcinogen"

"This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence, e.g., (a) a malignant tumor response in a single well-conducted experiment that does not meet conditions for sufficient evidence, (b) tumor responses of marginal statistical significance in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) responses of marginal statistical significance in a tissue known to have a high or variable background rate."

Group D: "Not Classifiable as to Human Carcinogenicity"

"This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available."

Group E: "Evidence of Non-Carcinogenicity for Humans"

"This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

The designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances."

NATURAL & MAN-MADE CHEMICALS

A COMMON MISCONCEPTION IS THAT ALL MAN-MADE CHEMICALS ARE HARMFUL, AND ALL NATURAL CHEMICALS ARE GOOD FOR US. HOWEVER, MANY NATURAL CHEMICALS ARE JUST AS HARMFUL TO HUMAN HEALTH, IF NOT MORE SO, THAN MAN-MADE CHEMICALS.

MUSCIMOL
FOUND IN FLY AGARIC MUSHROOMS

SOLANINE
FOUND IN GREEN POTATOES

ETHYLENE GLYCOL
USED IN ANTI-FREEZE

ASPIRIN
USED AS A PAIN-RELIEVING DRUG

AMYGDALIN
FOUND IN APPLE SEEDS

SODIUM THIOPENTAL
FORMERLY USED FOR LETHAL INJECTIONS

TOXIC EFFECTS SEEN AT 1000MG/KG OF BODY WEIGHT

NATURAL

MAN-MADE

ALL CHEMICALS CAN BE BROADLY DIVIDED INTO TWO CATEGORIES: NATURAL OR MAN-MADE

NO TOXIC EFFECTS SEEN AT 1000MG/KG OF BODY WEIGHT

SUCROSE
ALSO KNOWN AS TABLE SUGAR

TEFLON (PTFE)
USED IN NON-STICK PANS

CITRIC ACID
FOUND IN LEMONS & LIMES

WATER
ESSENTIAL FOR LIFE

PROPYLENE GLYCOL
FOOD ADDITIVE - SOLVENT, HUMECTANT & THICKENER

ASPARTAME
ARTIFICIAL SWEETENER

"EVERYTHING IS POISON, THERE IS POISON IN EVERYTHING. ONLY THE DOSE MAKES A THING NOT A POISON."

PARACELSUS, 1493-1541, 'THE FATHER OF TOXICOLOGY'