Recent Advances in Identifying the Causes of Cancer

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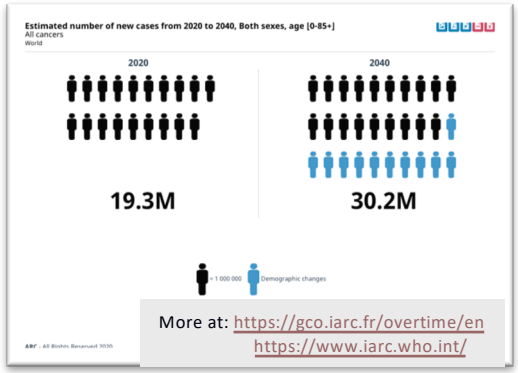
Conflict of Interest Statement

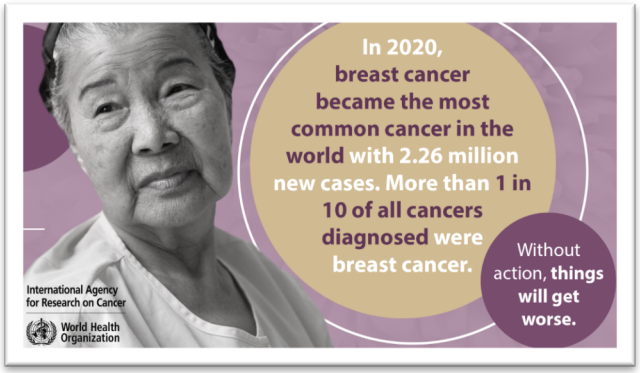
I declare no financial interests related to the subject matter of my presentation.

Presentation Overview

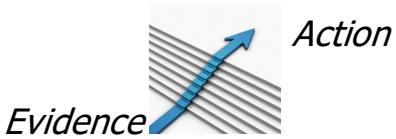
- Cancer: today and tomorrow
- Progress and promise in identifying cancer causes
- The key characteristics (KCs) of carcinogens: new insights into causes of cancer

Cancer: the Global Burden

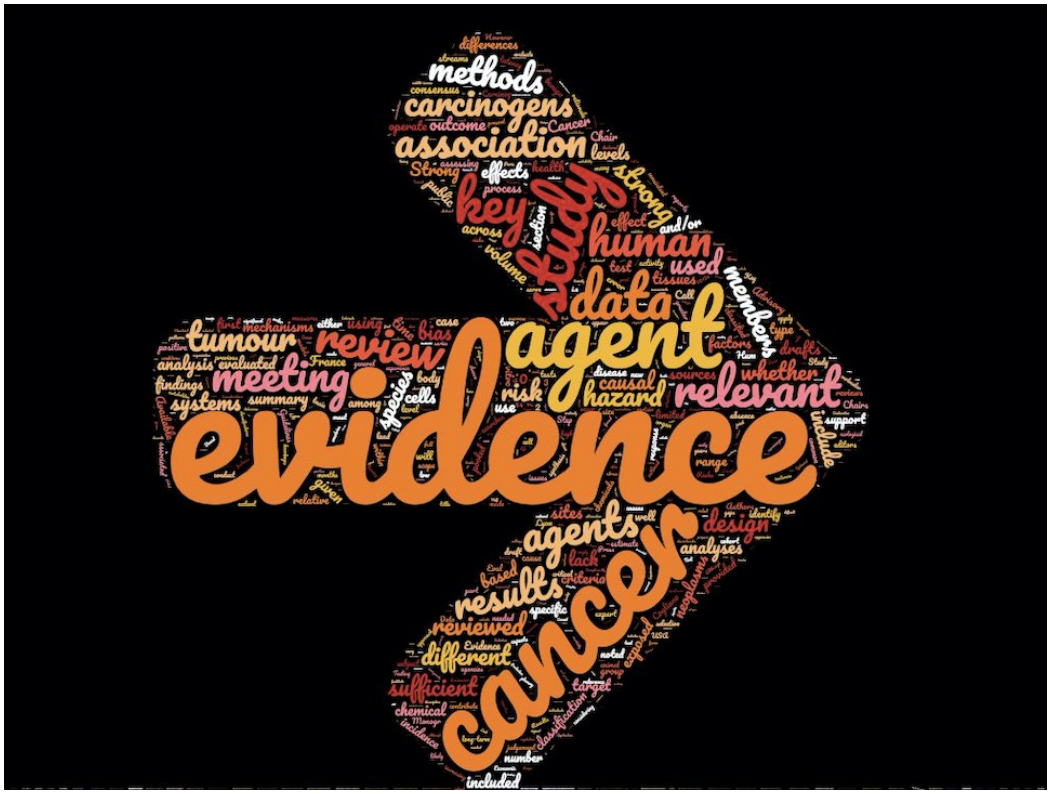




- Rising burden & changing demographics
- Prevention is the single most effective response to these challenges
- The first step in cancer prevention is to **identify the causes of human cancer**
- Authoritative reviews provide the scientific basis for action
  - Regulation to reduce exposures
  - Actions by individuals



How Are Carcinogens Identified?



Preamble to the IARC Monographs (amended January 2019):
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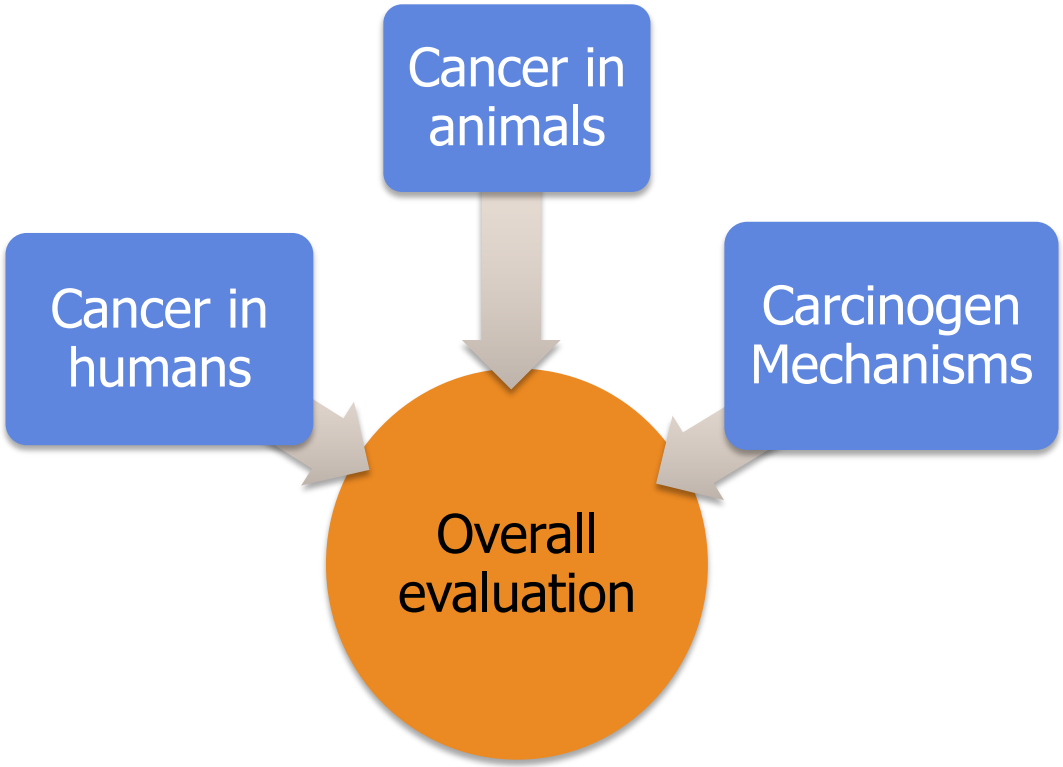

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How Are Overall Evaluations Reached?

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

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What Causes Cancer?

Agents Classified by the IARC Monographs, Volumes 1–130

Group 1	Carcinogenic to humans	121 agents
Group 2A	Probably carcinogenic to humans	90 agents
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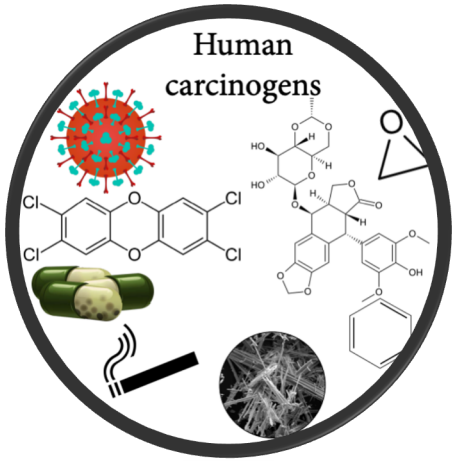
How Are Group 1 Agents Identified?

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficie		
Limited			sibly carcinogenic oup 2B)
	Sufficie		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Most Group 1 agents were identified from human (observational) studies

What Causes Cancer?



Group 1 carcinogens include:

- Chemicals
- Occupations
- Fibers
- Metals
- Pollutants/pollution
- Tobacco (smoking and secondhand)
- Radiation
- Drugs
- Viruses

https://monographs.iarc.who.int/agents-classified-by-the-iarc/

Human Cancer: Known Causes and Prevention by Organ Site

IARC Monographs on the Identification of Carcinogenic Hazards to Humans and Handbooks of Cancer Prevention

Monographs 1-130, Handbooks 1-18, updated 11 November 2021
Agents classified as carcinogenic to humans (Group 1) (in red)
Interventions with sufficient evidence of a cancer-preventive effect (in green)

Eye
Human immunodeficiency virus type 1
Ultraviolet emissions from welding
Ultraviolet-emitting tanning devices

Brain and central nervous system
X-radiation, gamma-radiation
Absence of excess body fatness (meningioma)

Lung
Acheson process (occupational exposure)
Aluminium production
Arsenic and inorganic arsenic compounds
Asbestos (all forms)
Beryllium and beryllium compounds
Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)
Cadmium and cadmium compounds
Chromium (VI) compounds
Coal, indoor emissions from household combustion
Coal gasification
Coal-tar pitch
Coke production
Diesel engine exhausts
Gamma-radiation
Haematite mining (underground)
Iron and steel founding
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
Nickel compounds
Opium (consumption of)
Outdoor air pollution
Outdoor air pollution, particulate matter in
Painter (occupational exposure as)
Plutonium
Quitting smoking
Radon-222 and its decay products
Rubber manufacturing industry
Silica dust, crystalline
Soot
Sulfur mustard
Tobacco smoke, secondhand
Tobacco smoking
Welding fumes
X-radiation

Nasal cavity and paranasal sinus
Isopropyl alcohol manufacture using strong acids
Leather dust
Nickel compounds
Radium-226 and its decay products
Radium-228 and its decay products
Tobacco smoking
Wood dust

Oral cavity
Alcoholic beverages
Betel quid with tobacco
Betel quid without tobacco
Human papillomavirus type 16
Quitting smoking
Smokeless tobacco
Tobacco smoking

Pharynx (oro-, hypo- and/or NOS)
Alcoholic beverages
Betel quid with tobacco
Human papillomavirus type 16
Quitting smoking
Tobacco smoking

Nasopharynx
Epstein–Barr virus
Formaldehyde
Salted fish, Chinese-style
Wood dust

Tonsil
Human papillomavirus type 16

Salivary gland
X-radiation, gamma-radiation

Larynx
Acid mists, strong inorganic
Alcoholic beverages
Asbestos (all forms)
Opium (consumption of)
Quitting smoking
Tobacco smoking

Thyroid
Absence of excess body fatness
Radioiodines, including iodine-131 (exposure during childhood and adolescence)
X-radiation, gamma-radiation

Pleura or peritoneum (mesothelioma)
Asbestos (all forms)
Erionite
Fluoro-edenite fibrous amphibole
Painter (occupational exposure as)

Breast
Alcoholic beverages
Absence of excess body fatness (postmenopausal)
Diethylstilbestrol
Estrogen–progestogen contraceptives
Estrogen–progestogen menopausal therapy
Mammography screening (50–74 years)
Regular physical activity
X-radiation, gamma-radiation

Stomach
Absence of excess body fatness (gastric cardia)
Helicobacter pylori
Quitting smoking
Rubber manufacturing industry
Tobacco smoking
X-radiation, gamma-radiation

Upper aerodigestive tract
Acetaldehyde associated with consumption of alcoholic beverages

Oesophagus
Acetaldehyde associated with consumption of alcoholic beverages
Alcoholic beverages
Absence of excess body fatness (adenocarcinoma)
Betel quid with tobacco
Betel quid without tobacco
Quitting smoking (squamous cell carcinoma)
Smokeless tobacco
Tobacco smoking
X-radiation, gamma-radiation

Liver (hepatocellular carcinoma)
Absence of excess body fatness
Aflatoxins
Alcoholic beverages
Estrogen–progestogen contraceptives
Hepatitis B virus
Hepatitis C virus
Plutonium
Thorium-232 and its decay products
Tobacco smoking (in smokers and in smokers' children)

Liver (angiosarcoma)
Vinyl chloride

Gall bladder
Absence of excess body fatness
Thorium-232 and its decay products

Biliary tract
1,2-Dichloropropane
Clonorchis sinensis
Opisthorchis viverrini

Colon and rectum
Alcoholic beverages
Absence of excess body fatness
Regular physical activity
Processed meat (consumption of)
Screening with gFOBT
Screening with FIT
Screening with sigmoidoscopy
Screening with colonoscopy
Tobacco smoking
X-radiation, gamma-radiation

Pancreas
Absence of excess body fatness
Quitting smoking
Smokeless tobacco
Tobacco smoking

Anus
Human immunodeficiency virus type 1
Human papillomavirus type 16

Urinary bladder
Aluminium production
4-Aminobiphenyl
Arsenic and inorganic arsenic compounds
Auramine production
Benzidine
Chlornaphazine
Cyclophosphamide
Magenta production
2-Naphthylamine
Opium (consumption of)
Painter (occupational exposure as)
Quitting smoking
Rubber manufacturing industry
Schistosoma haematobium
Tobacco smoking
ortho-Toluidine
X-radiation, gamma-radiation

Kidney
Absence of excess body fatness
Quitting smoking
Tobacco smoking
Trichloroethylene
X-radiation, gamma-radiation

Renal pelvis and ureter
Aristolochic acid, plants containing
Phenacetin
Phenacetin, analgesic mixtures containing
Tobacco smoking

Corpus uteri (endometrium)
Absence of excess body fatness
Estrogen menopausal therapy
Estrogen–progestogen menopausal therapy
Tamoxifen

Uterine cervix
Conventional cytology screening
Diethylstilbestrol (exposure in utero)
Estrogen–progestogen contraceptives
Human papillomavirus nucleic acid (DNA or mRNA) testing
Human immunodeficiency virus type 1
Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Liquid-based cytology screening
Quitting smoking
Tobacco smoking

Vagina
Diethylstilbestrol (exposure in utero)
Human papillomavirus type 16

Vulva
Human papillomavirus type 16

Ovary
Absence of excess body fatness
Asbestos (all forms)
Estrogen menopausal therapy
Tobacco smoking

Bone
Plutonium
Radium-224 and its decay products
Radium-226 and its decay products
Radium-228 and its decay products
X-radiation, gamma-radiation

Penis
Human papillomavirus type 16

Leukaemia/lymphoma
Absence of excess body fatness (multiple myeloma)
Azathioprine
Benzene
Busulfan
1,3-Butadiene
Chlorambucil
Cyclophosphamide
Cyclosporine
Epstein–Barr virus
Etoposide with cisplatin and bleomycin
Fission products, including strontium-90
Formaldehyde
Helicobacter pylori
Hepatitis C virus
Human immunodeficiency virus type 1
Human T-cell lymphotropic virus type 1
Kaposi sarcoma herpesvirus
Lindane
Melphalan
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
Pentachlorophenol
Phosphorus-32, as phosphate
Rubber manufacturing industry
Semustine [1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, or methyl-CCNU]
Thiotepa
Thorium-232 and its decay products
Tobacco smoking
Treosulfan
X-radiation, gamma-radiation

Multiple sites (unspecified)
Cyclosporine
Fission products, including strontium-90
X-radiation, gamma-radiation (exposure in utero)

All cancers combined
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin

Skin (melanoma)
Polychlorinated biphenyls
Solar radiation
Ultraviolet-emitting tanning devices

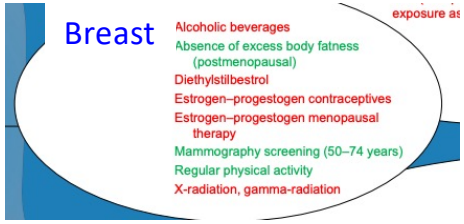
Skin (other malignant neoplasms)
Arsenic and inorganic arsenic compounds
Azathioprine
Coal-tar distillation
Coal-tar pitch
Cyclosporine
Methoxsalen plus ultraviolet A
Mineral oils, untreated or mildly treated
Shale oils
Solar radiation
Soot
X-radiation, gamma-radiation

Endothelium (Kaposi sarcoma)
Human immunodeficiency virus type 1
Kaposi sarcoma herpesvirus

Group 1 agents with less than sufficient evidence in humans
2,3,4,7,8-Pentachlorodibenzofuran
Polychlorinated biphenyls with a WHO TEF ("dioxin-like")
4,4′-Methylenebis(2-chloroaniline) (MOCA)
Alpha- and beta-particle emitters
Areca nut
Aristolochic acid
Benzidine, dyes metabolized to
Benzo[*a*]pyrene
Ethanol in alcoholic beverages
Ethylene oxide
Etoposide
Ionizing radiation (all types)
Neutron radiation
N′-Nitrosonornicotine (NNN) and 4-(*N*-nitroso-methylamino)-1-(3-pyridyl)-1-butanone (NNK)
Ultraviolet radiation

International Agency for Research on Cancer
World Health Organization

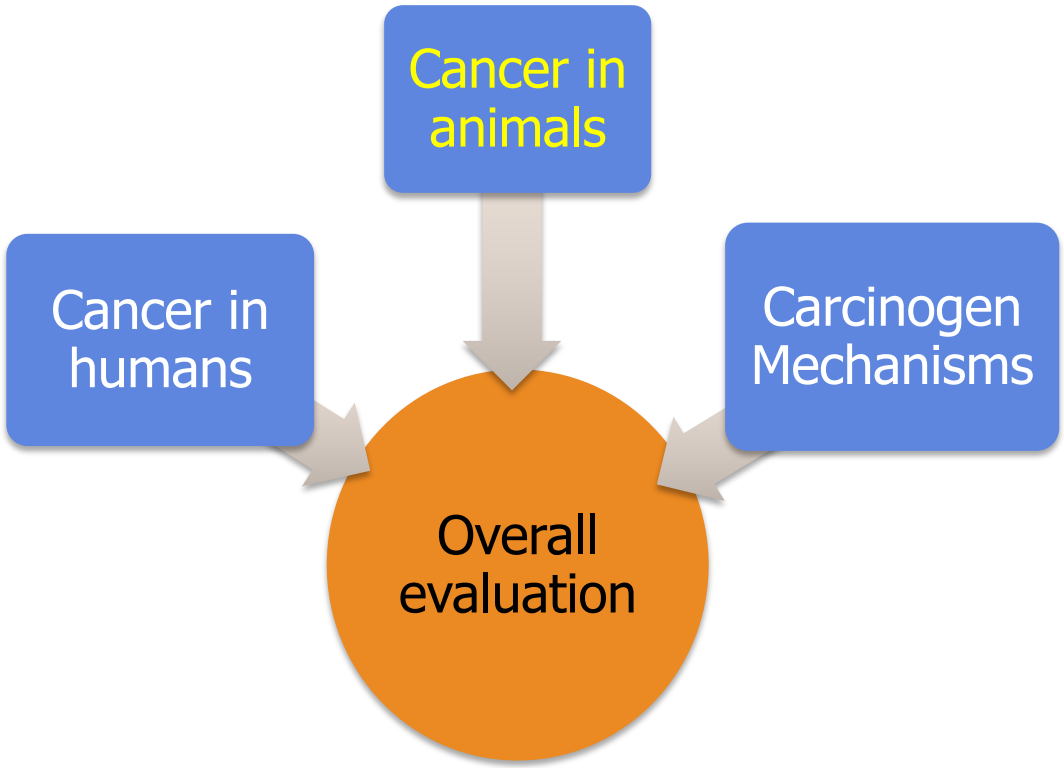
What Is Known across Cancer Types?



- Very few Group 1 breast carcinogens identified
  - Most occupational studies limited for women's cancers
  - Studies: dietary, medical, pharmaceutical setting

KZ Guyton & MK. Schubauer-Berigan, *Environ. Health Perspect., 2021*
https://ehp.niehs.nih.gov/doi/10.1289/EHP9507

What Is the Role of Animal Data?



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Most Group 2B Agents Were Identified from Animal Bioassays

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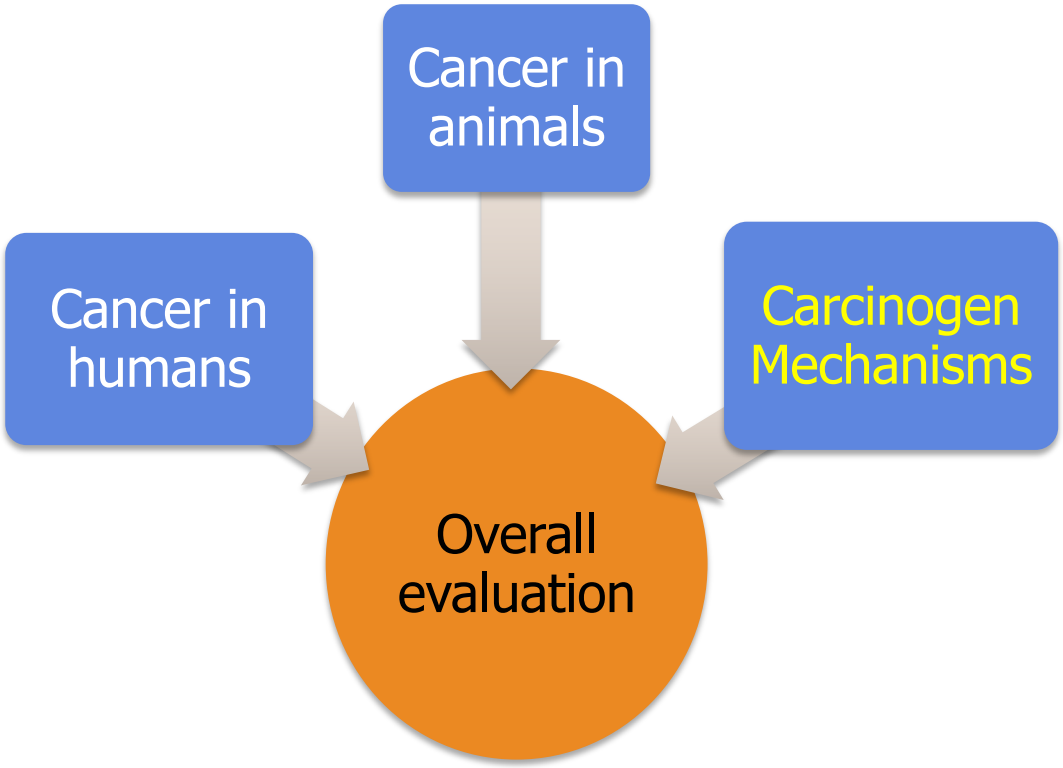
What Is the Role of Mechanistic Data?



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Chemicals in Commerce and Their Evaluation

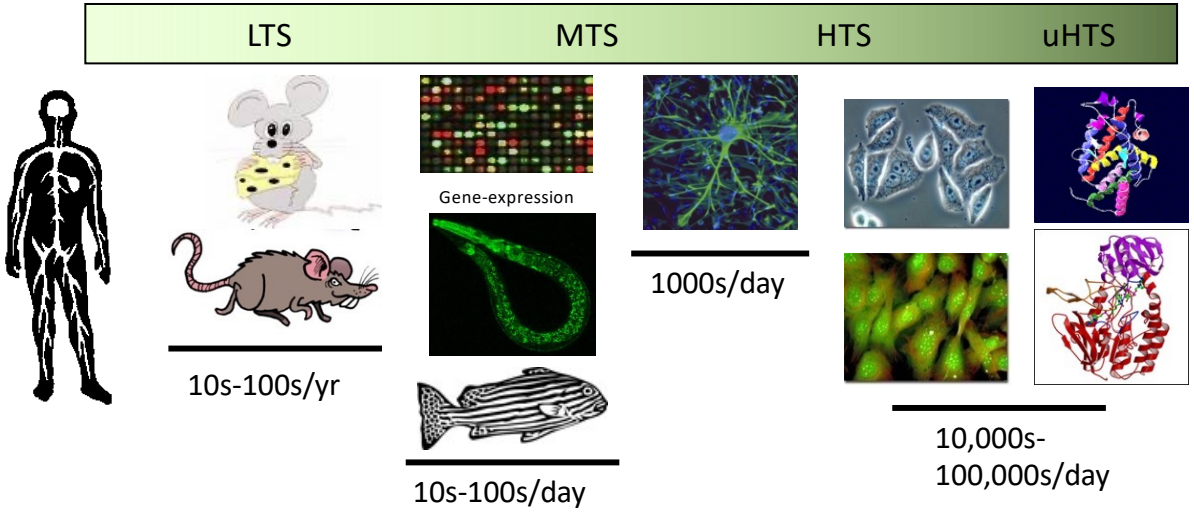
Chemicals in US commerce	
On Toxic Substances Control Act Chemical Substance Inventory	~75,000
Chemicals in US commerce between 25,000 – 1,000,000 lbs/yr	6500-7000
Chemicals in US commerce >1,000,000 lbs/yr	>2200
Notable publicly available reviews	
Number of chemicals evaluated by IARC	>900
Number of chemicals listed on IRIS	545
Number of chemicals reviewed by Center for the Evaluation of Risks to Human Reproduction (CERHR)	23
Proposition 65 list of carcinogens and reproductive toxicants	~775

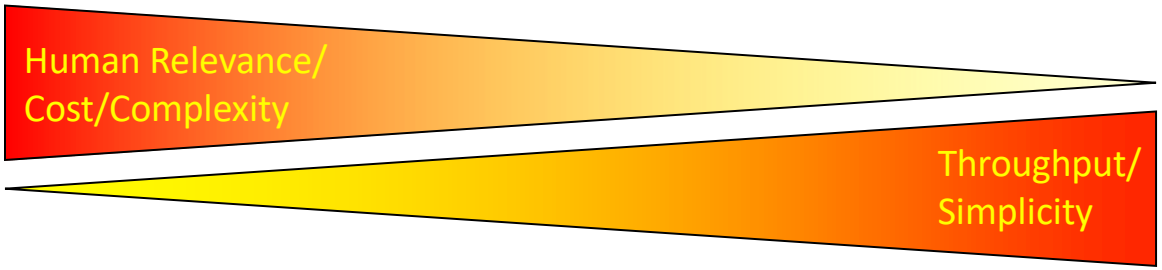
Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, Keshava N, Sandy MS, Sonawane B, Zhang L, Waters MD and Smith MT. Mutat Res. 681(2-3):230-40, 2009.

Challenges in Identifying Carcinogens

- No assessment = no hazard?
- How to select and prioritize agents for assessment?
- Can mechanistic evidence help to fill gaps?

Diverse Sources of Mechanistic Data



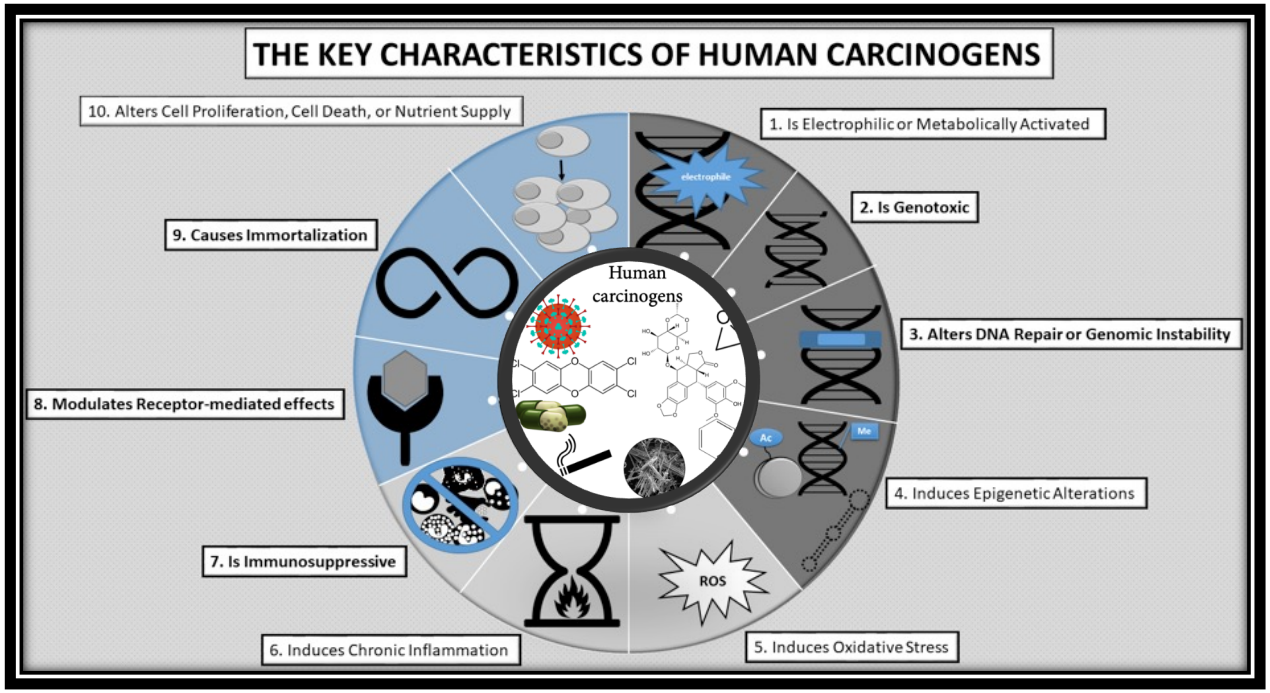


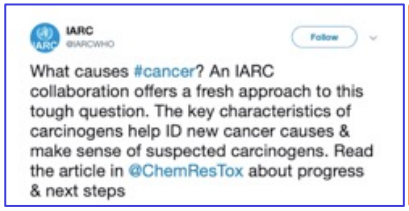
What Are the Mechanisms of Human Carcinogens?

	Carcinogen				
Mechanisms	**Aflatoxin B1**	**Arsenic**	**Asbestos**	**Benzene**	**DES**
DNA damage	+	+	-	+	+
Gene mutation	+	-	+	-	-
Chrom mutation	+	+	+	+	+
Aneuploidy	-	+	+	+	+
Epigenetic	+	+		+	+
Receptor signaling	-	+	+		+
Other signaling	-	+		+	+
Immune effects	+	+	+	+	+
Inflammation	+	+	+	+	
Cytotoxicity	+	+	+	+	-
Mitogenic	-	+		-	+
Gap junction	+	+		+	+

Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, Keshava N, Sandy MS, Sonawane B, Zhang L, Waters MD and Smith MT. Mutat Res. 681(2-3):230-40, 2009.

New Insights for Identifying Cancer Causes





- Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K (2016). Env Health Persp., 124(6):713-21.
- Guyton KZ, Rieswijk L, Wang A, Chiu WA, Smith MT (2018). Chemical Research in Toxicology, 31(12): 1290-1292.
- For more on the key characteristics of hazardous exposures, see: https://keycharacteristics.org/

Mechanistic Data Can Be Pivotal When Human Data Are Not Sufficient

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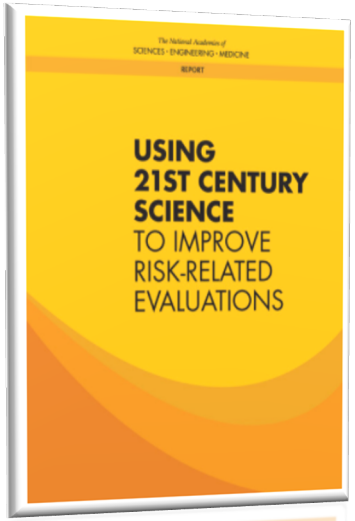
Guidance from the US National Academies of Sciences



https://www.nap.edu/download/24635

- The "[KCs] approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence."
- "The committee notes that key characteristics for other hazards, such as cardiovascular and reproductive toxicity, could be developed as a guide for evaluating the relationship between perturbations observed in assays, their potential to pose a hazard, and their contribution to risk."

For more on the key characteristics of hazardous exposures, see: https://keycharacteristics.org/

Thank ***<u>you</u>***!


thank you
danke
謝謝
ngiyabonga
شكراً جزيلاً
teşekkür ederim
спасибо
Баярлалаа
рахмат
gracias
tapadh leat
хвала
mochchakkeram
go raibh maith agat
dziękuję
bedankt
obrigado
sukriya
kop khun krap
terima kasih
감사합니다
ありがとう
arigatō
grazie
dakujem
мерси
takk
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sagolun
hvala
mauruuru
dank je
merci
ευχαριστώ