

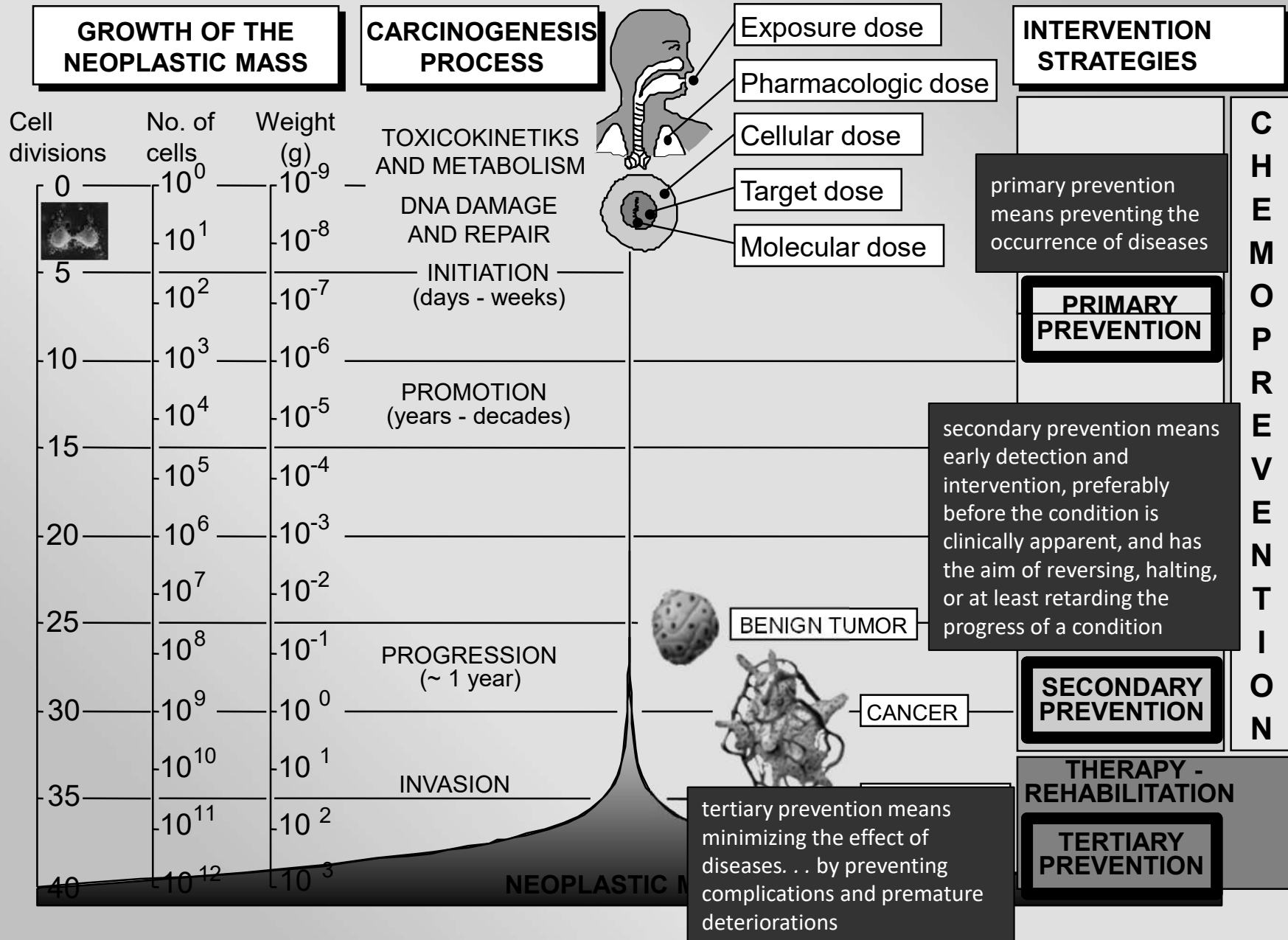
PROTECTIVE MECHANISMS AND CANCER PREVENTION.

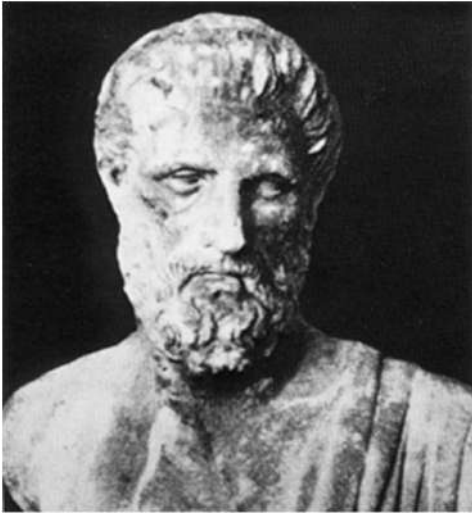
What lesson from research on chromium?

Silvio De Flora

**Department of Health Sciences
University of Genoa**







Hippocrates



Asclepius

Panacea Hygeia

**RISK
FACTORS**

DISEASES

RF 1

D 1

RF 2

D 2

RF 3

D 3

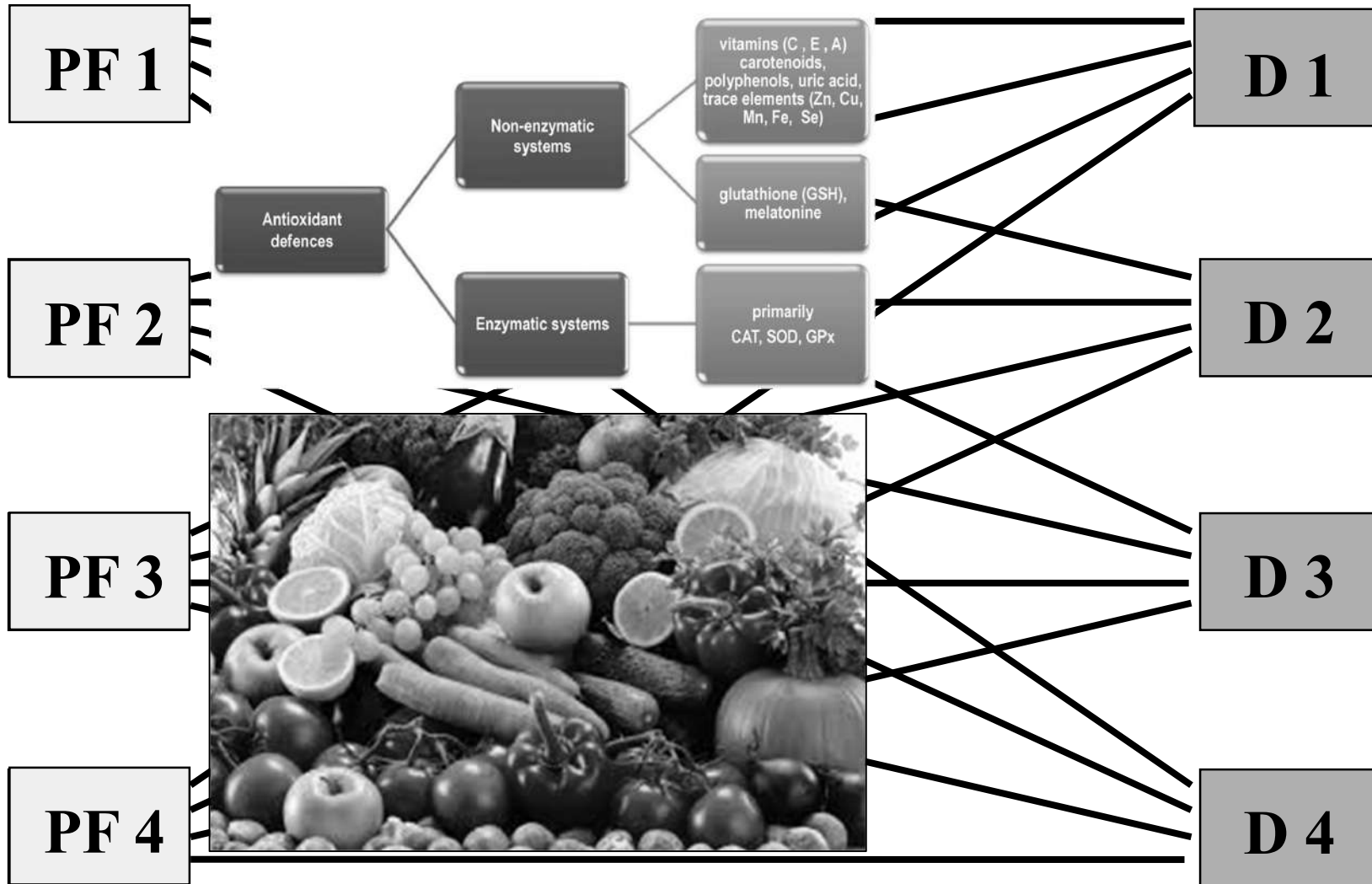
RF 4

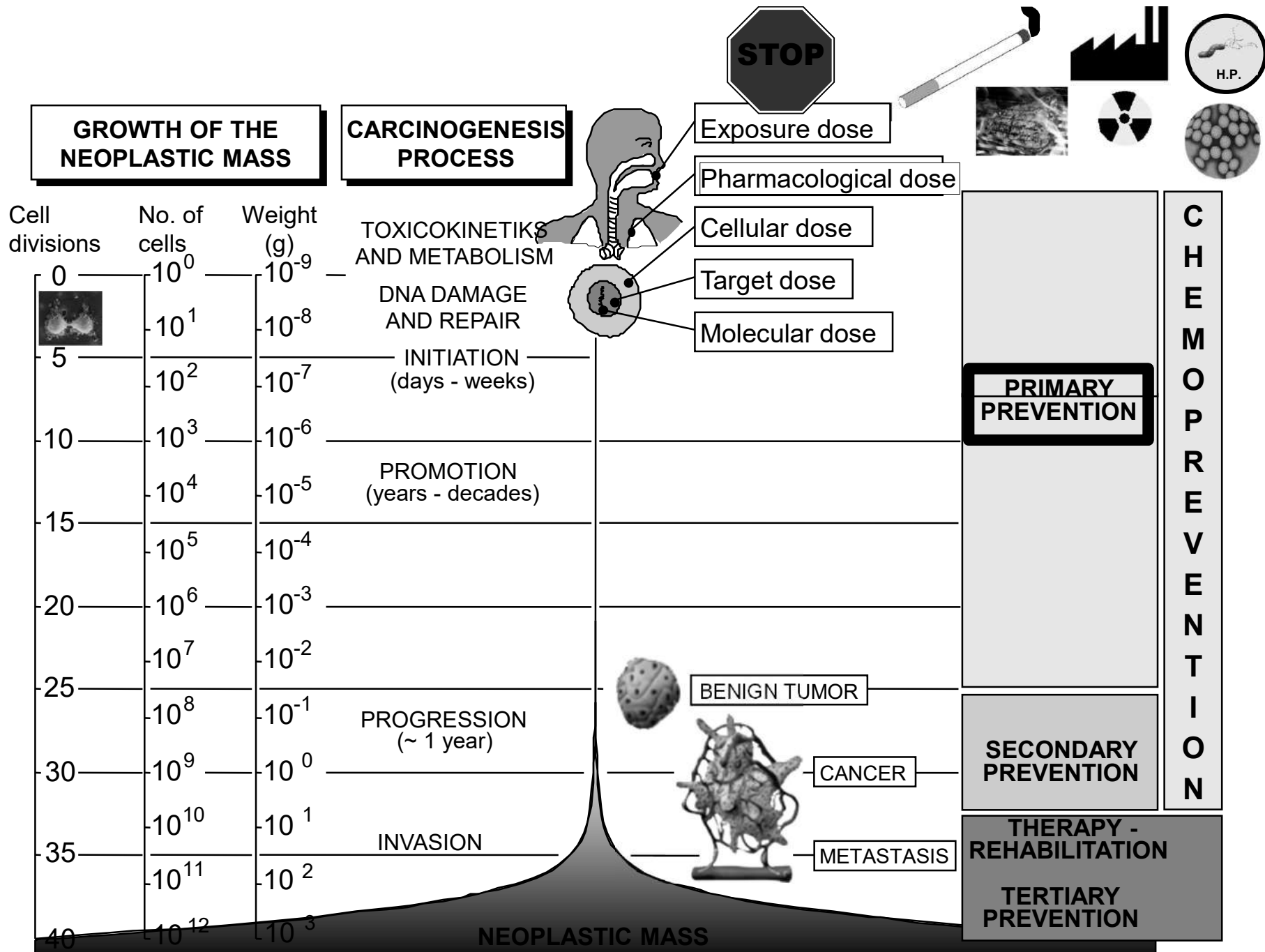
D 4



PROTECTIVE FACTORS

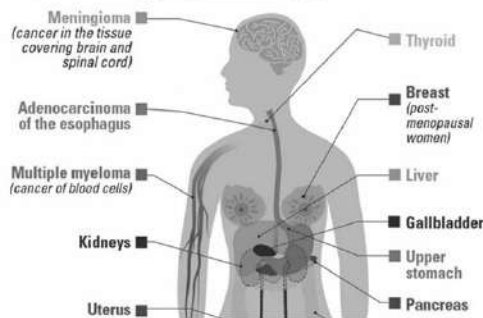
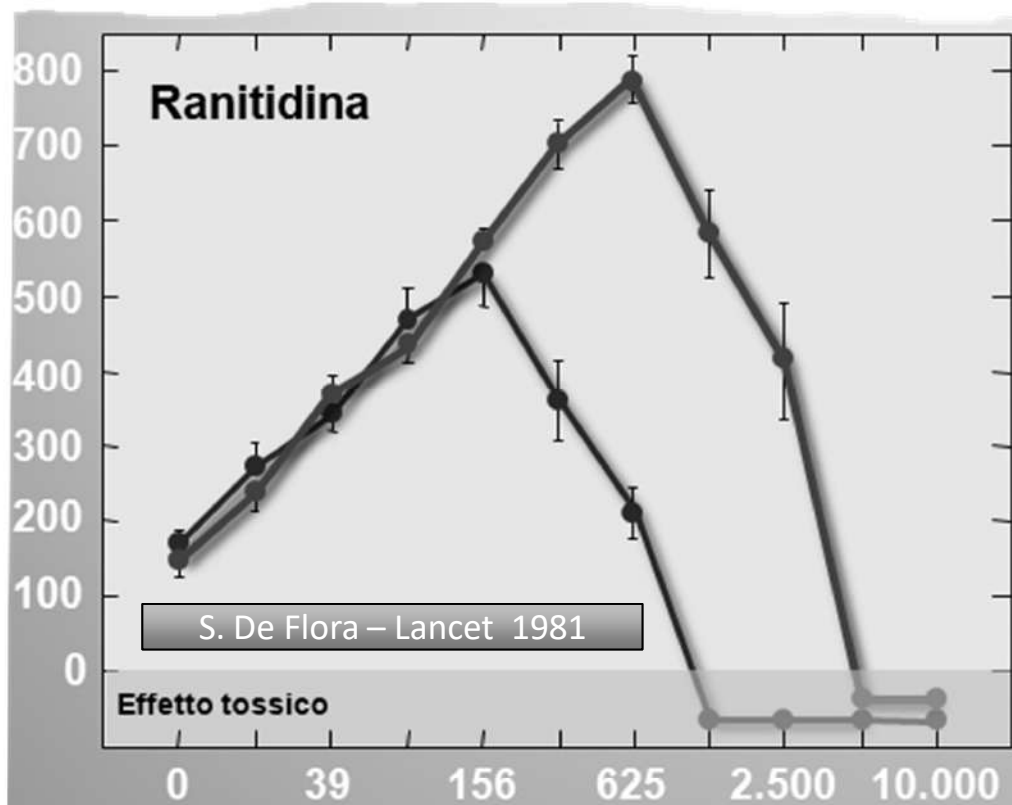
DISEASES





DIETA, ALIMENTAZIONE E CANCRO

FATTORI DI RISCHIO



FATTORI PROTETTIVI



ATTIVITA' FISICA REGOLARE

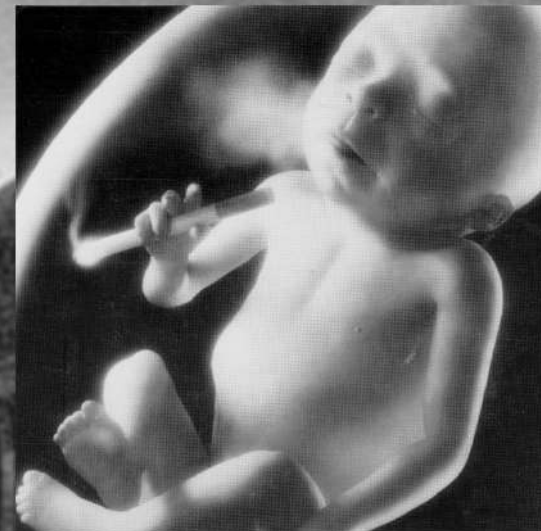
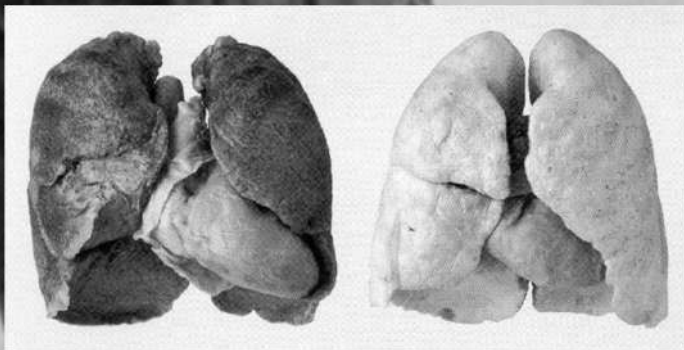
2 - 3 volte a settimana
20 - 30 minuti

vari composti protettivi (crucifere)
Fibre indigeribili
Prodotti lattiero-caseari fermentati
Frutta e verdura, bevande (vino, thé)

**MAINSTREAM
SMOKE**

**SIDESTREAM
SMOKE**

**ENVIRONMENTAL
CIGARETTE
SMOKE (ECS)**



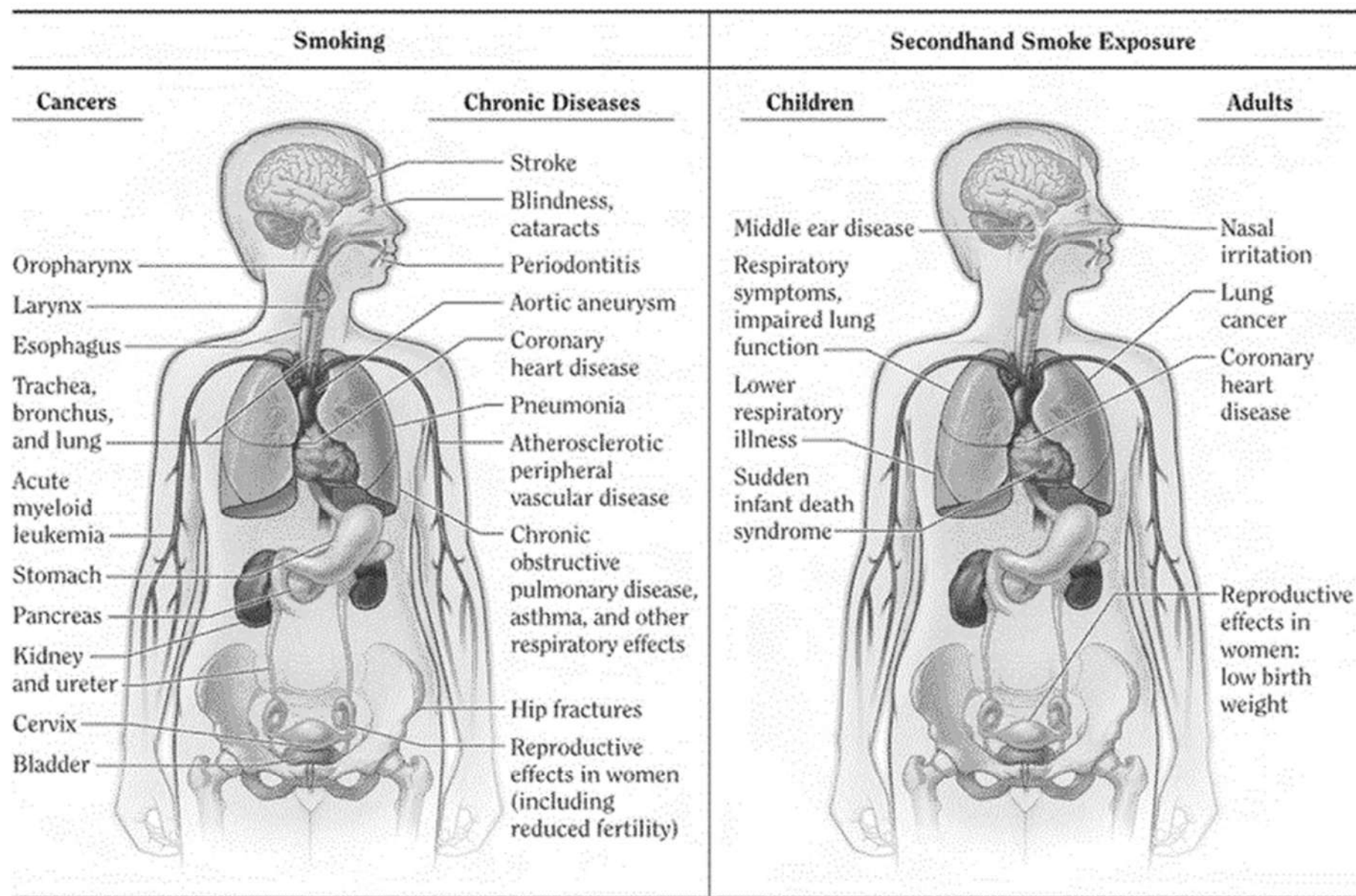


Figure 1.1 The health consequences causally linked to smoking and exposure to secondhand smoke

Source: USDHHS 2004, 2006.

THE PREVENTION OF INFECTION-ASSOCIATED CANCERS

(S. De Flora and P. Bonanni, *Carcinogenesis* 32, 787-795, 2011)

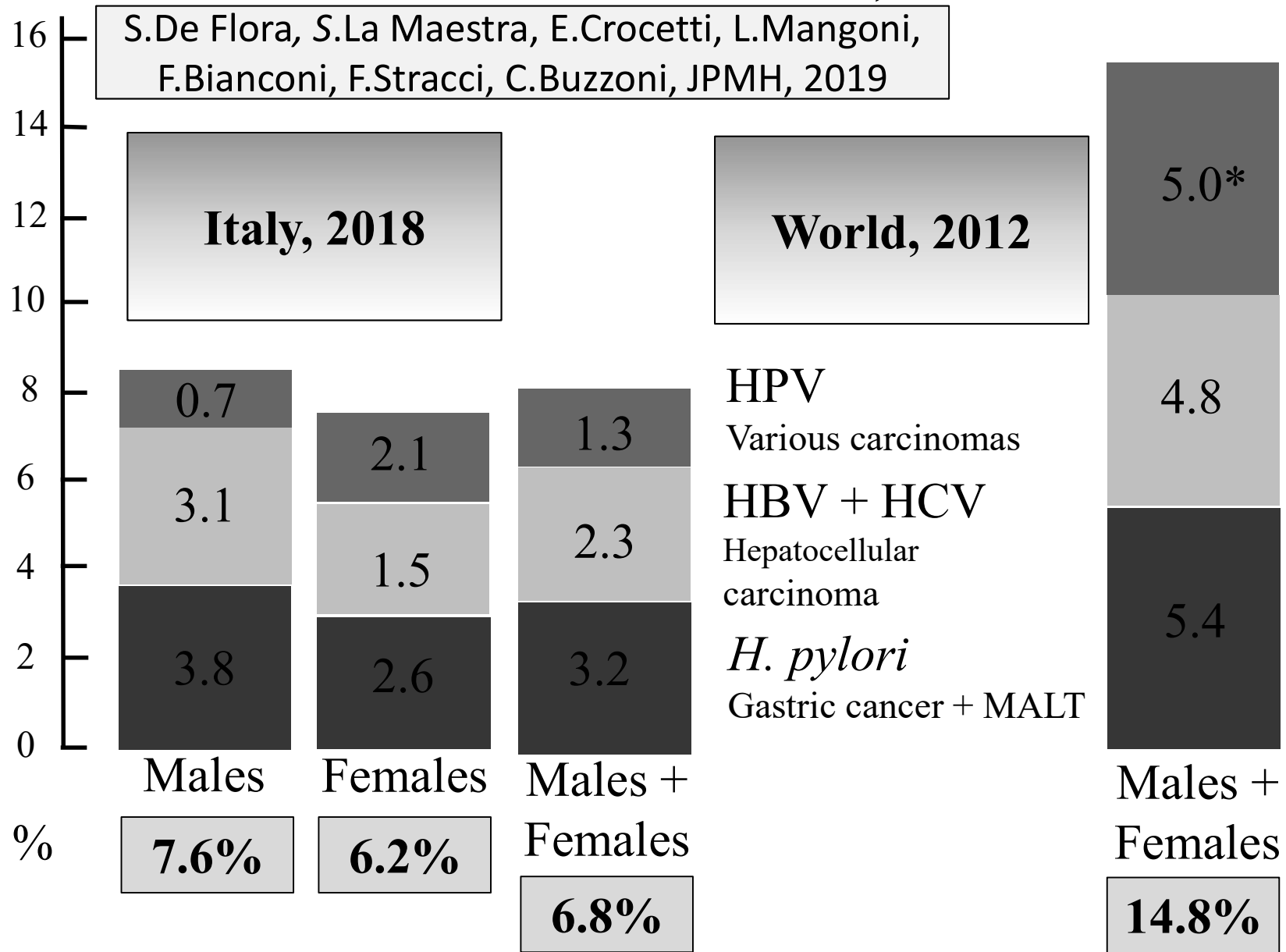
Pathogen	IARC Group	Main associated cancer
Hepatitis viruses		
HBV	1	Hepatocellular carcinoma
HCV	1	Hepatocellular carcinoma
HDV	3	None
Papillomaviruses HPV		
α HPV type 16	1	Cancers at several sites
α HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	1	Cervical cancer
α HPV type 68	2A	Cervical cancer
α HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97	2B	Cervical cancer
β HPV type 5 and 8	2B	Skin cancer
α HPV type 6 and 11	3	None
Other β and γ HPV types	3	None
Polyomaviruses		
JCV	NA	CNS tumors and colorectal cancer?
MCV	NA	Skin cancer (Merkel cell carcinoma)
SV40	NA	Malignant mesothelioma ?
Herpesviruses		
EBV or HHV4	1	Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma
KSHV or HHV8	1	Kaposi's sarcoma, primary effusion lymphoma

Pathogen	IARC Group	Main associated cancer
Retroviruses		
HTLV-I	1	Adult T-cell leukemia/lymphoma
HTLV-II	3	None
HIV-I	1	Kaposi's sarcoma, non-Hdgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anus cancer, conjunctive cancer
HIV-II	2B	Kaposi's sarcoma, non-Hodgkin's lymphoma
HERV-K	NA	Human breast cancer
Helicobacter pylori	1	Gastric cancer, MALT
Schistosomes		
<i>S. haematubium</i>	1	Urinary bladder cancer
<i>S. japonicum</i>	2B	Colorectal and liver cancers
<i>S. mansoni</i>	3	None
Liver flukes		
<i>Opistorchis viverrini</i>	1	Cholangiocarcinoma
<i>Opistorchis felineus</i>	3	None
<i>Chlonorchis sinensis</i>	1	Cholangiocarcinoma

Infectious agents cause 17% of all cancers worldwide, 26% in developing world, 8% in developed world

D.M. Parkin, *Int.J.Cancer* 15, 3030-44, 2005

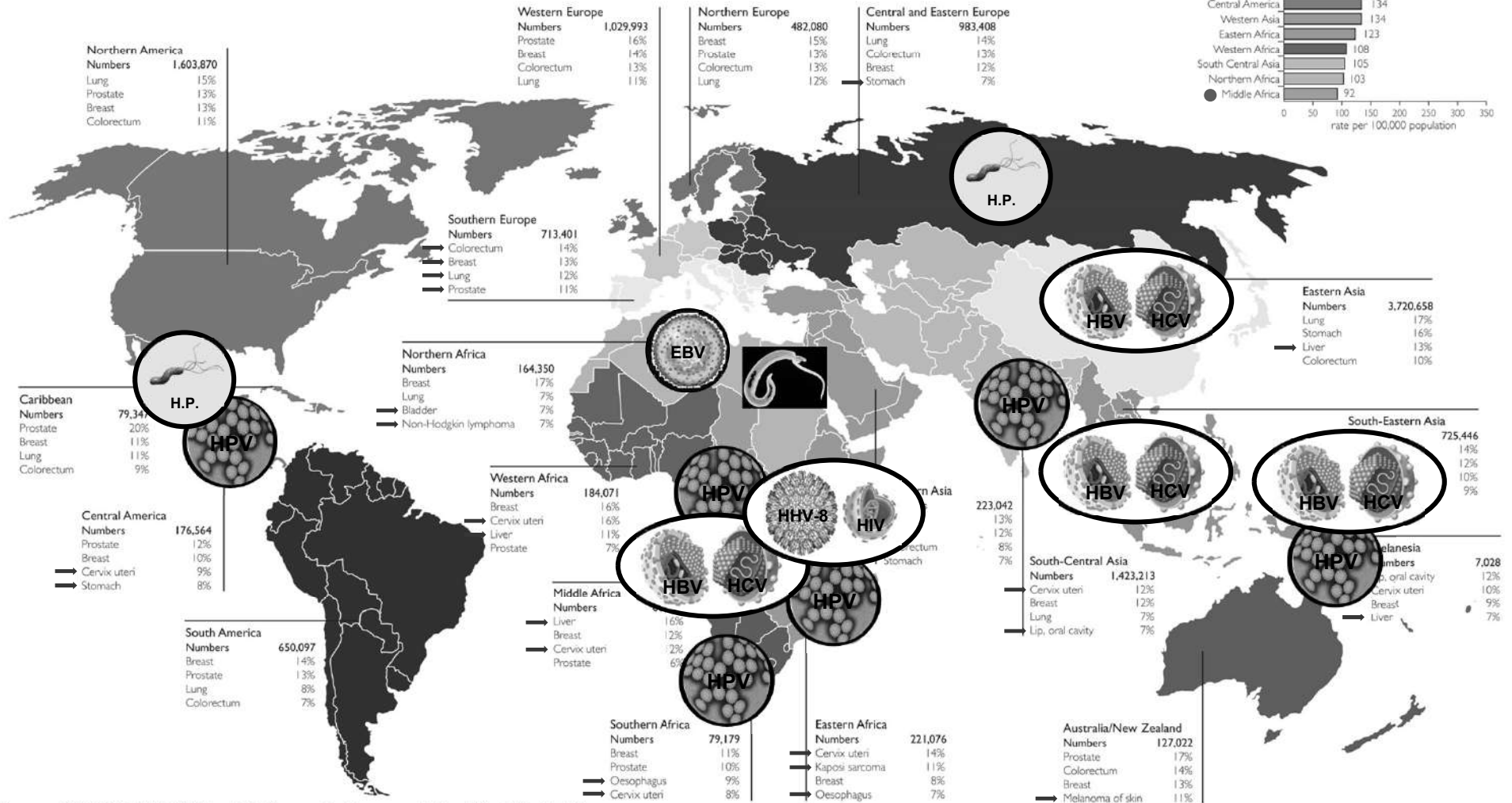
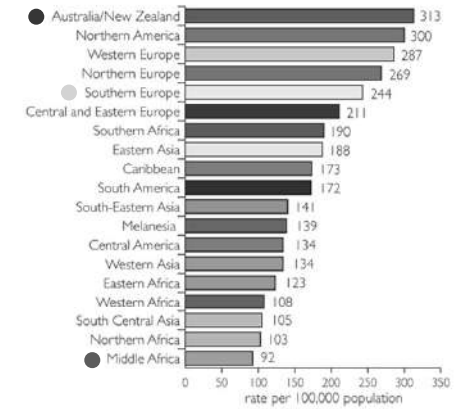
CANCERS ATTRIBUTABLE TO *H. PYLORI*, HBV/HCV AND HPV



*Cervix only

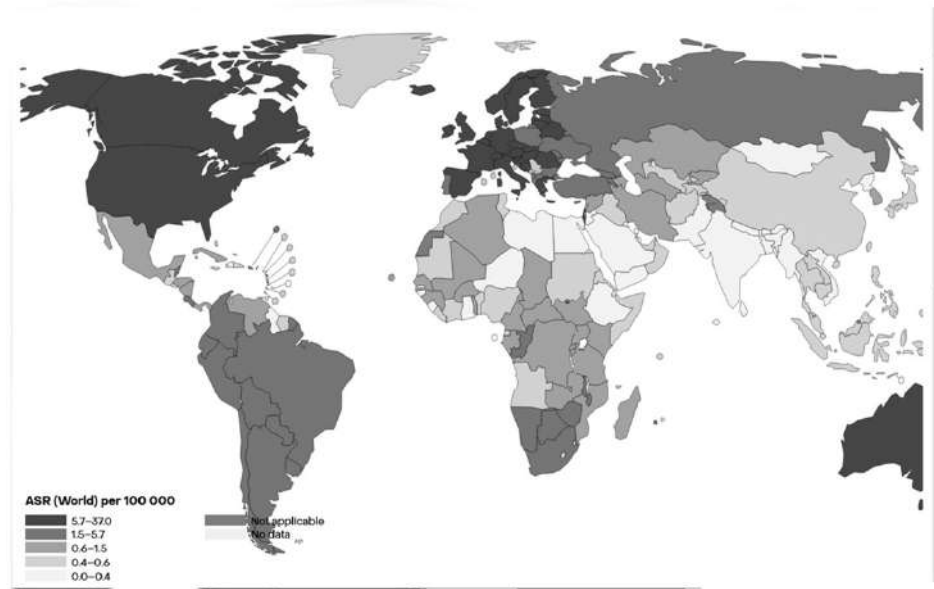
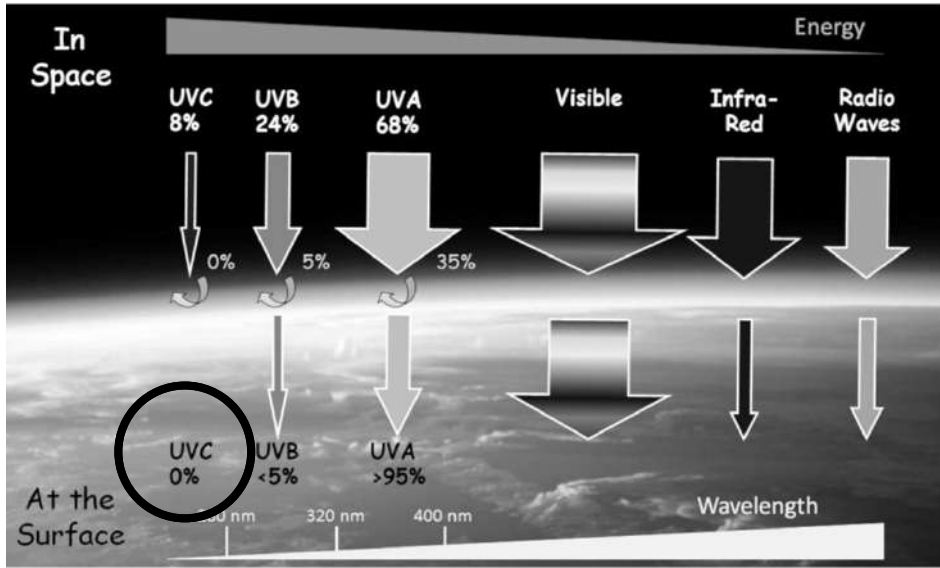
Cancer Incidence Worldwide

Breakdown of the estimated 12.7 million new cases, World-age standardised incidence rates and the most commonly diagnosed cancers by the different regions of the world, 2008.



Source: GLOBOCAN 2008, v. 1.2, Cancer Incidence and Mortality Worldwide. IARC, 2010 (<http://globocan.iarc.fr>)
Map updated February 2011

<http://info.cancerresearchuk.org/cancerstats/>



**Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022
Melanoma of skin
IARC, WHO**



CARCINOGENICITY OF THE LIGHT EMITTED BY HALOGEN LAMPS



Arrivano le lampadine ad alogeni
OSRAM HALOSTAR UV STOP.

La ricerca scientifica conferma che un normale vetro è sufficiente per offrire protezione dai raggi ultravioletti emessi dalle lampadine ad alogeni. OSRAM ha voluto fare di più. Le nuove HALOSTAR UV STOP hanno infatti uno speciale bulbo in quarzo che assorbe alla sorgente le radiazioni UV-C e UV-B e riduce del 50% le UV-A. Una soluzione innovativa per sorgenti luminose che offrono in tutta tranquillità gli effetti brillanti e decorativi tipici dell'illuminazione ad alogeni. Per assicurare all'ambiente in cui vivi o lavori il comfort e la bellezza di una luce nuova, inserisci subito nella tua lampada ad alogeni un OSRAM HALOSTAR UV STOP. La puoi richiedere al tuo rivenditore di fiducia.

SPECIALISTI IN LUCE **OSRAM**

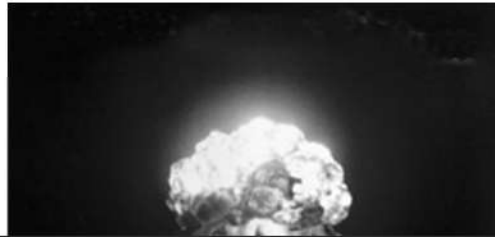
**ULTRAVIOLETTI,
ADDIO!**

S. De Flora & F. D' Agostini, Nature 356, 569, 1992

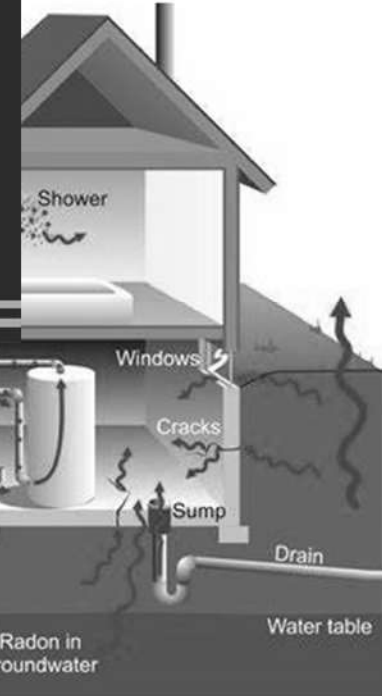
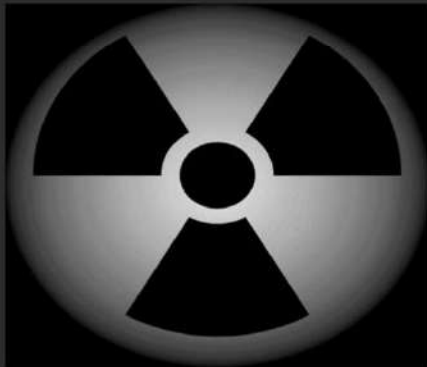
ACCIDENTS AT NUCLEAR POWER PLANTS



FALL-OUT RADIOATTIVO



RADIOPROTECTION



Alimentary restriction
in human thyroids

*P. Orlando, G. Gallelli, F. Perdelli
& S. De Flora*

*reprinted from
nature, 6 November 1986*

Agenti cancerogeni in Lista I del Ministero del Lavoro

(G.U. 19/03/2010, n. 65)

Polmone

Asbesto, Berillio, (Bis)Clorometilene, Cadmio, Nickel, Cromo(VI), IPA, TCDD, Radon, Silice, Fumo passivo

Pleura

Asbesto, Erionite

Cavità nasali e seni paranasali

Nickel, Cromo(VI)

Nasofaringe

Formaldeide

Fegato

Arsenico, Cloruro di vinile, HBV, HCV

Vescica

Ammine aromatiche, IPA

Cute

Arsenico, IPA, Radiazioni solari

Sistema emolinfopoietico

Benzene, 1,3-Butadiene, Ossido di etilene, Radiazioni ionizzanti

Linfomi

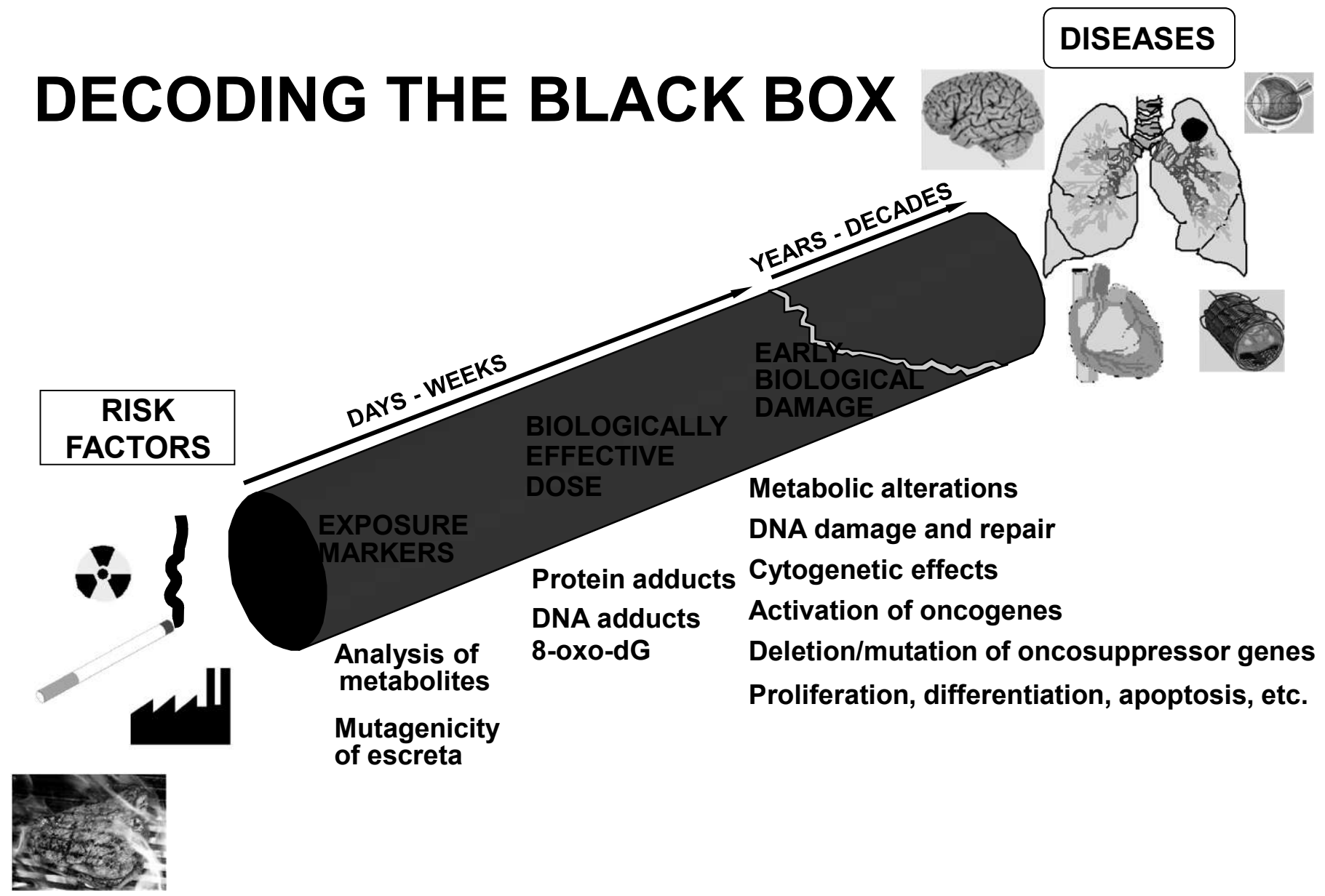
TCDD, HIV

Sarcomi

TCDD, HIV



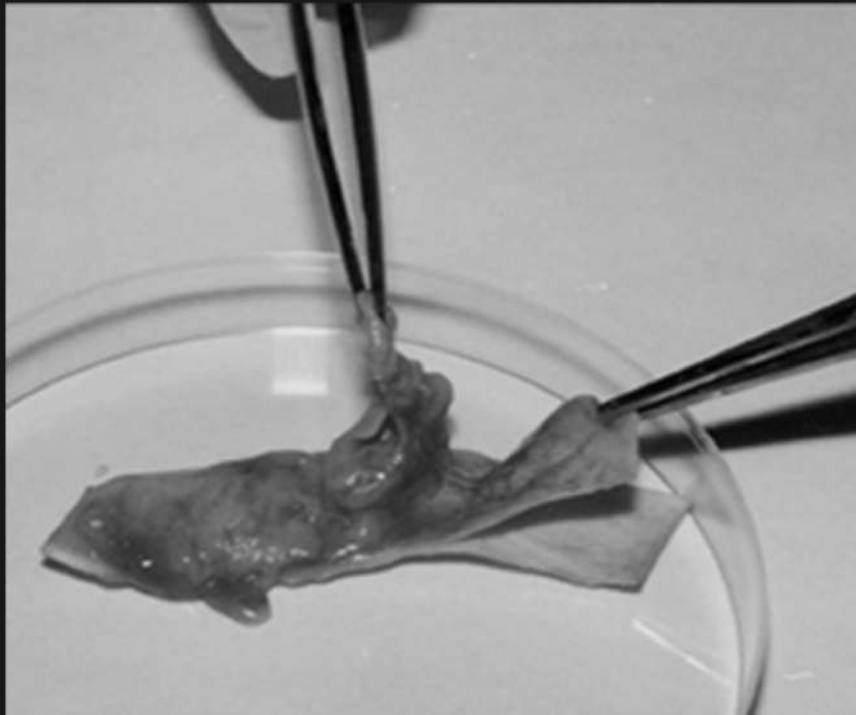
DECODING THE BLACK BOX



MOLECULAR EPIDEMIOLOGY OF ATHEROSCLEROSIS

S. De Flora et al., FASEB J. 11: 1021-1031, 1997

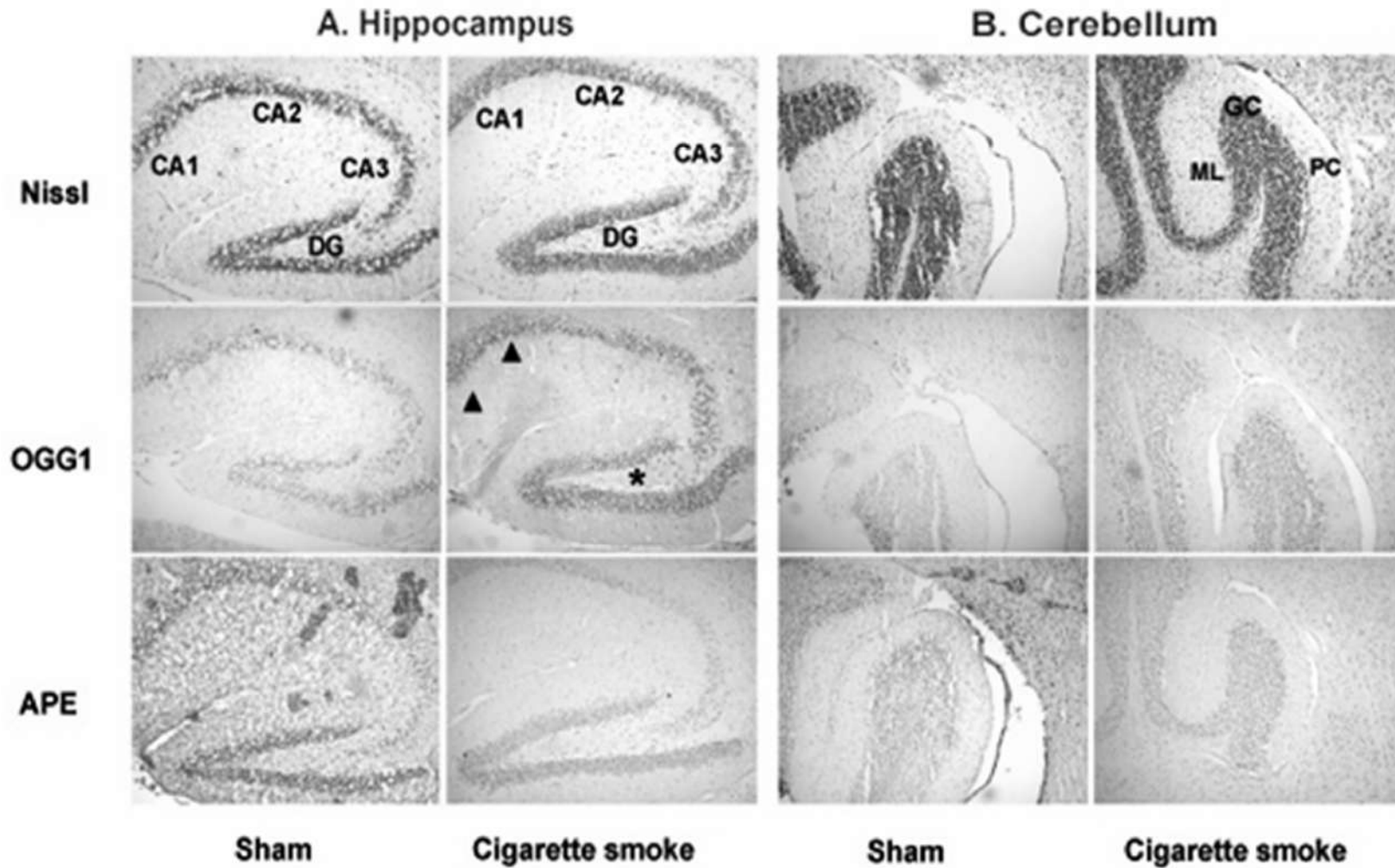
The levels of ^{32}P postlabeled DNA adducts in the aorta from 85 atherosclerotic patients were significantly correlated with:



- Age of patients
- Number of cigarettes
- High blood pressure
- Blood triglycerides
- Blood cholesterol (total/HDL)
- SFS-positive DNA adducts
- 8-Oxo-dGuo

DNA DAMAGE, DNA REPAIR, AND TAU ALTERATIONS IN MOUSE BRAIN

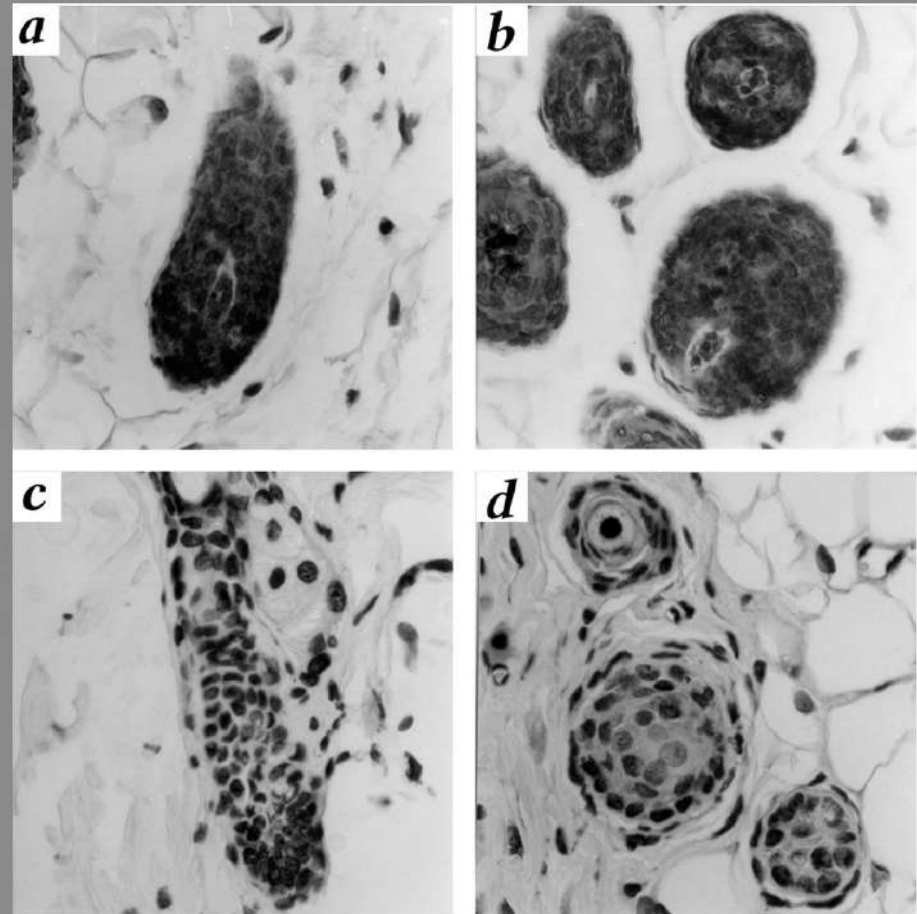
S. La Maestra et al., Toxicol. Sci., 2011



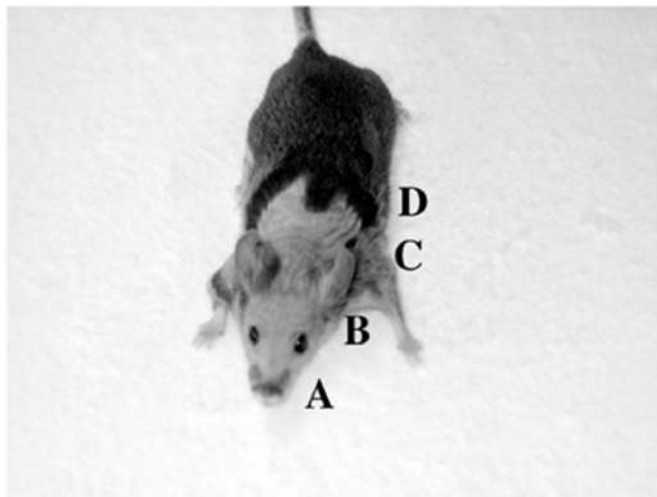
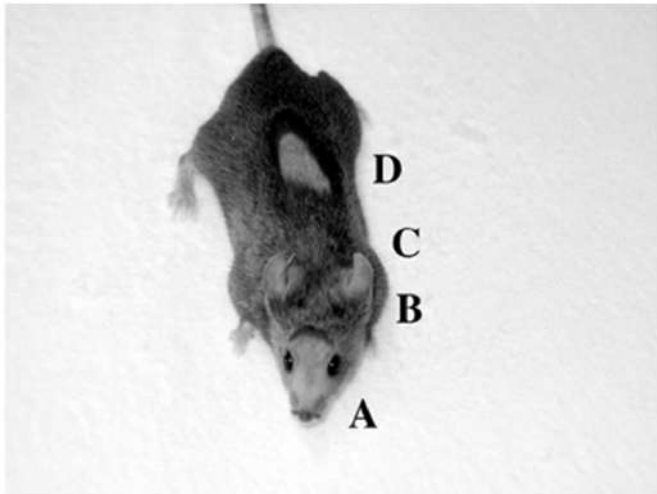
ALOPECIA AND GRAY HAIR IN MICE EXPOSED TO ENVIRONMENTAL CIGARETTE SMOKE (ECS)



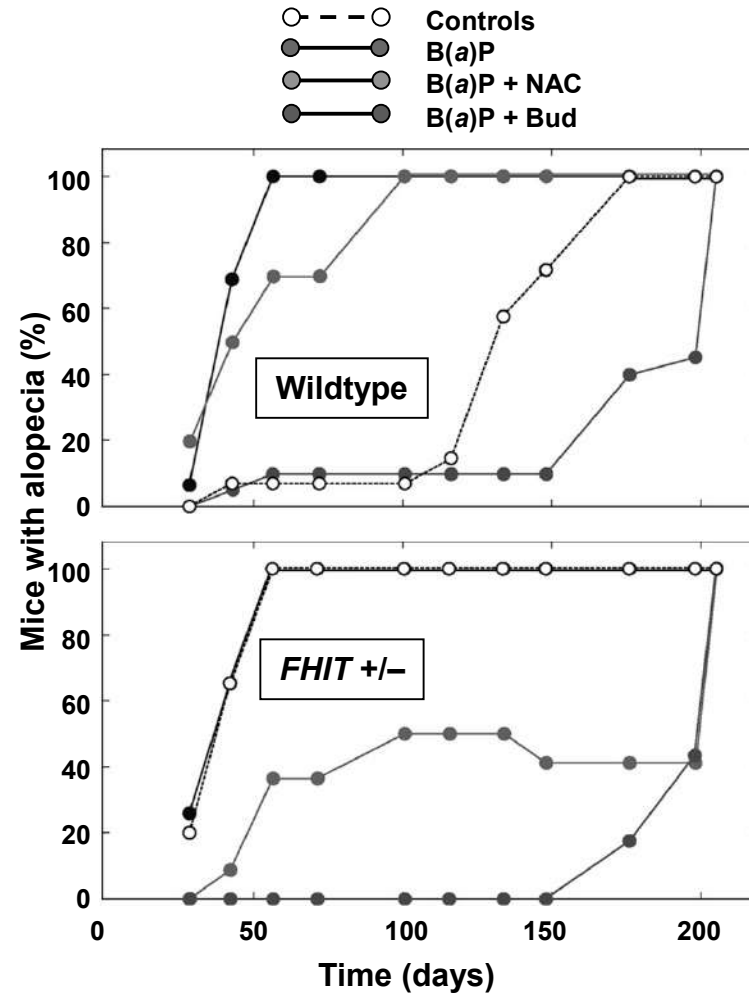
ECS

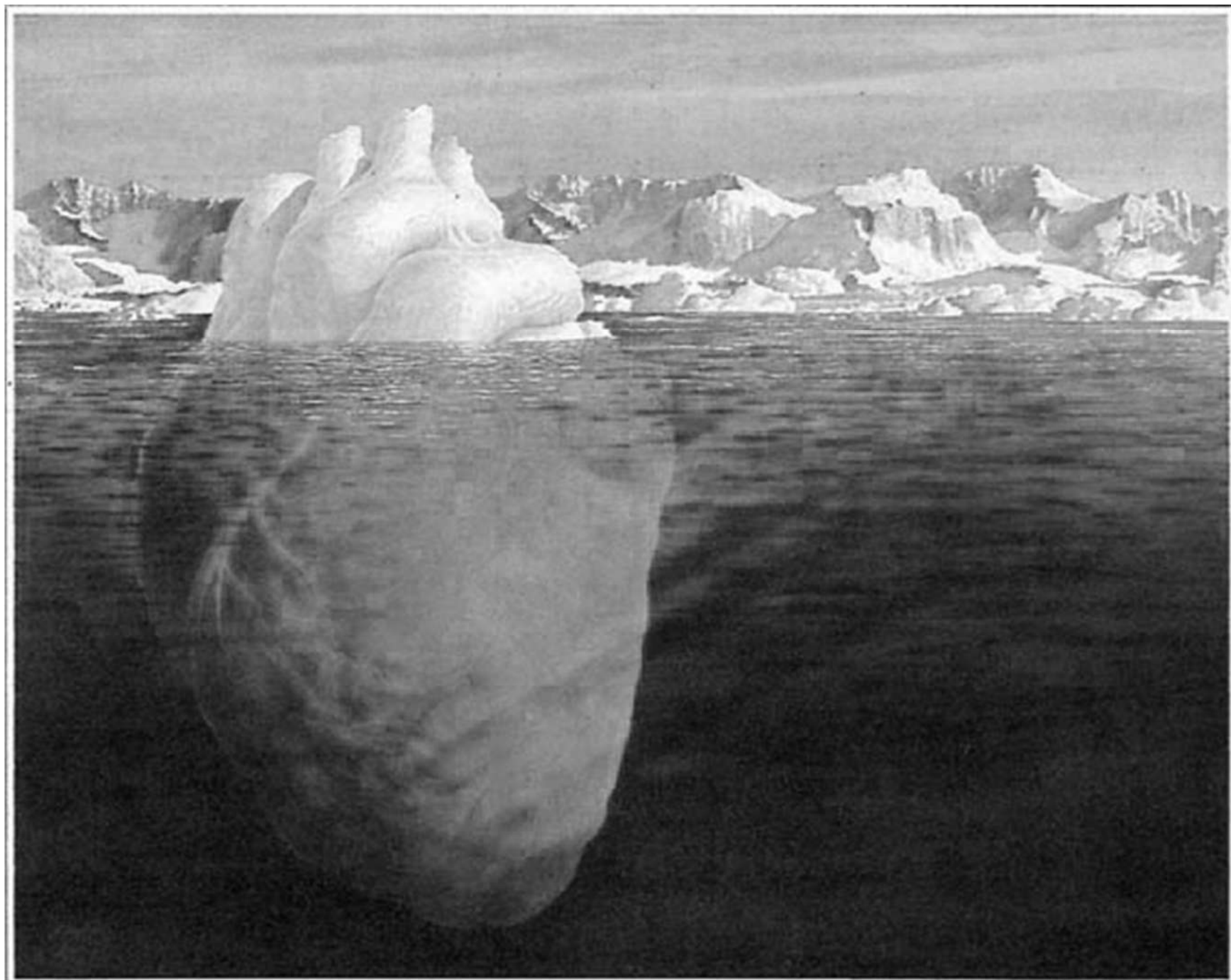


TIME COURSE FORMATION OF ALOPECIA IN B6-129(F1) MICE



Alopecia in the muzzle (A), head (B), neck (C), and back (D)



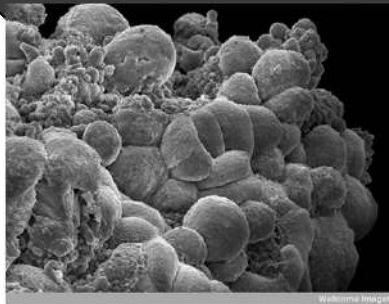


PROLIFERATION AND CHRONIC DEGENERATIVE DISEASES

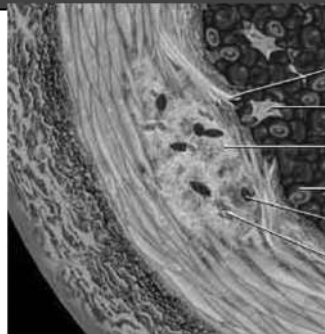
Genetic predisposition
DNA damage and repair
Oxidative stress
Chronic inflammation
Epigenetic mechanisms

Proliferation

Cancer



Atherosclerotic plaque



Degenerative diseases of the myocardium



Neurodegenerative diseases



Anticancer drugs

Anthracyclines and anthraquinolones

Capecitabine, Cytarabine, 5-Fluorouracil

Paclitaxel, Vinca alkaloids

Cyclophosphamide

TK Inhibitors (Trastuzumab, Imatinib, Bevacizumab, Sorafenib, Sunitinib, etc)

COX-2 inhibitors

Estrogen receptor modulators

Irradiation to the thorax

Mechanisms of cardiotoxicity

Mitochondrial dysfunction

Apoptosis of cardiomyocytes

ROS generation

DNA damage

Endothelial cell damage

Antibody directed cellular cytotoxicity

ATP block

Cell signaling, survival block

Fibrosis

Hypertension

Sinus bradycardia

Atrium-ventricular block

Ventricular tachycardia

Arrhythmias

Thromboembolism

Protective agents

ACE inhibitors

Beta-blockers

Statins

Dexrazoxane

L-Carnitine

Coenzyme Q10

N-Acetyl-L-Cysteine

Glutathione

Erdosteine

Selenium

Zinc

Melatonin

Flavonoids and polyphenols

Platelet antiaggregants

**A. Albini, G. Pennesi, R. Cammarota, F. Donatelli, S. De Flora*, D.M. Noonan*,
Cardiotoxicity of anticancer drugs: The need for cardio-oncology and
cardio-oncological prevention, J. Natl Cancer Inst., 102, 14-25, 2010**

DIAGNOSIS

THERAPY

**CARDIOVASCULAR
DISEASES**

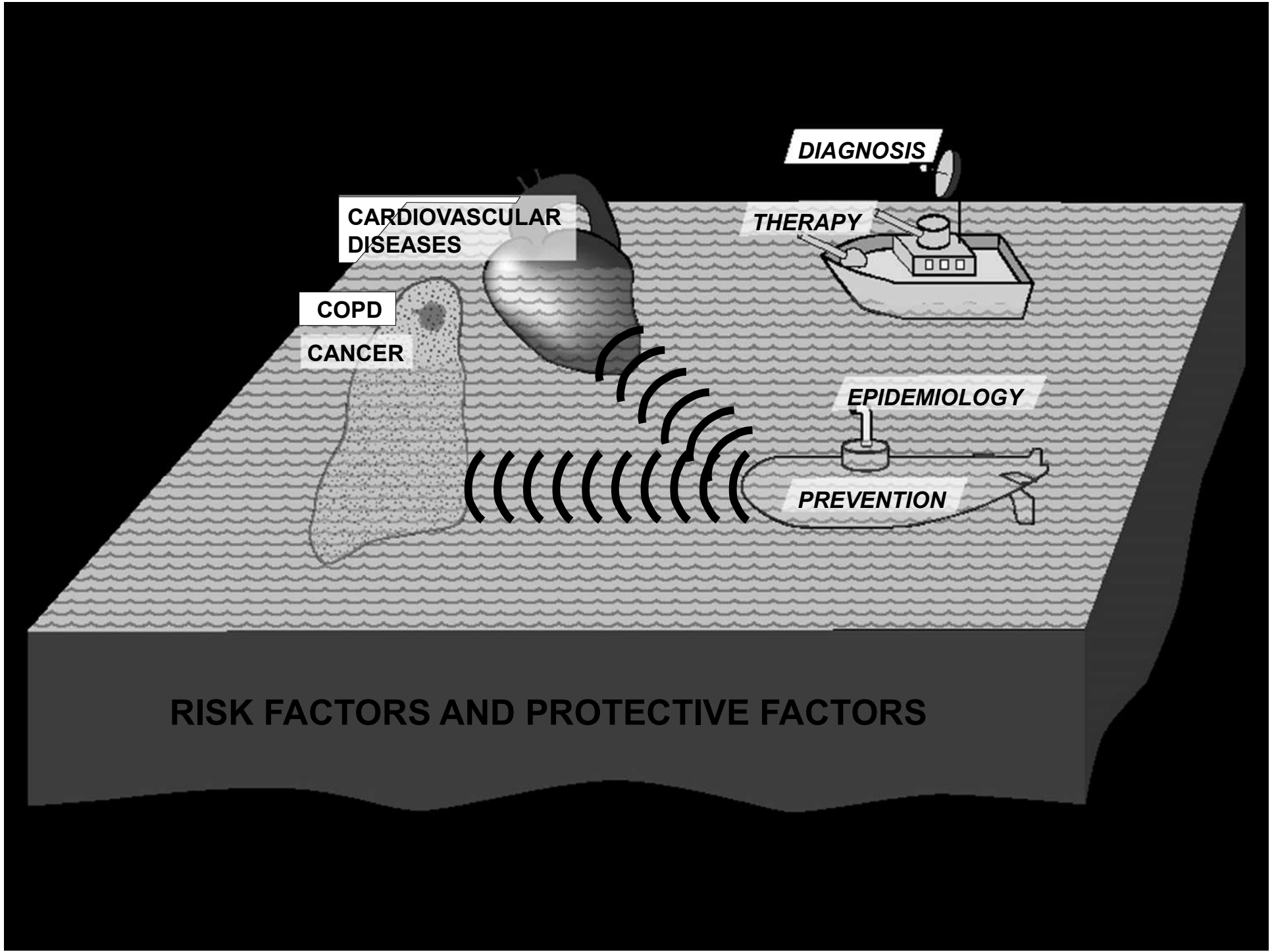
COPD

CANCER

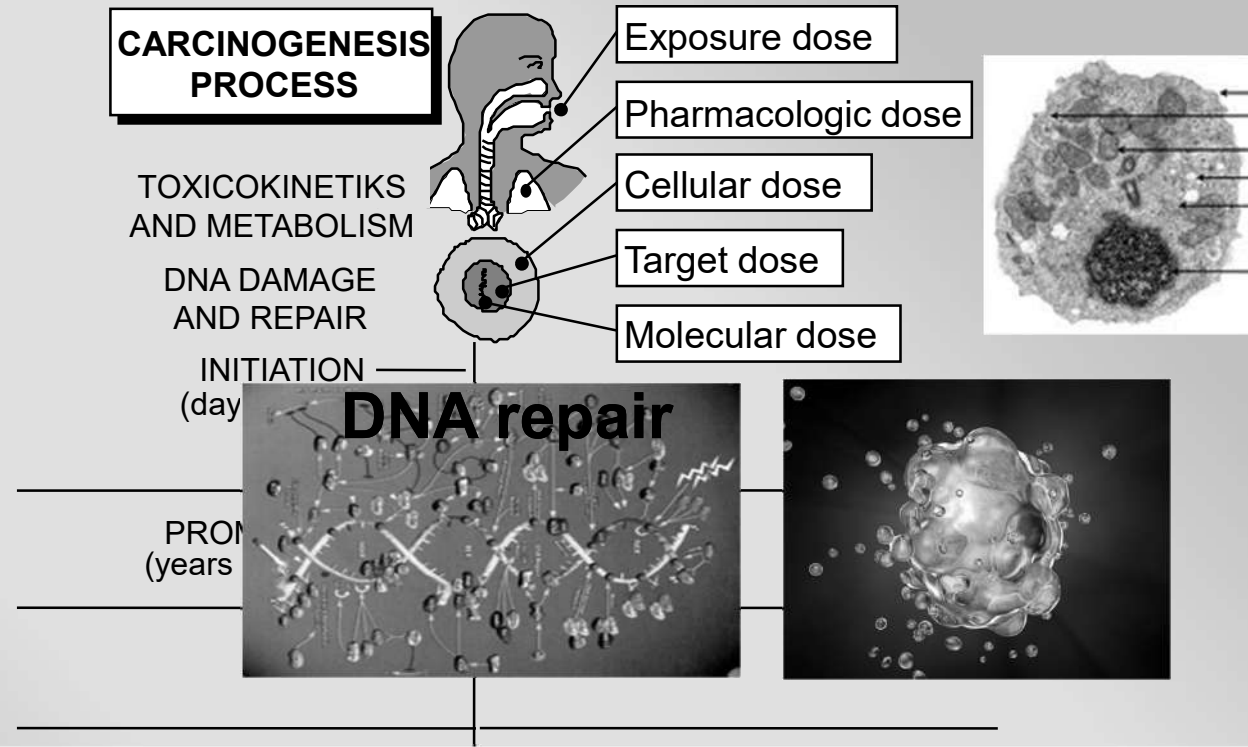
EPIDEMIOLOGY

PREVENTION

RISK FACTORS AND PROTECTIVE FACTORS



THRESHOLDS IN CARCINOGENESIS?



Med Lav. 2023; 114(1): e2023001.

PMCID: PMC9987469

Published online 2023 Feb 14. doi: [10.23749/mdl.v114i1.14176](https://doi.org/10.23749/mdl.v114i1.14176)

PMID: [36790404](https://pubmed.ncbi.nlm.nih.gov/36790404/)

The Linear Non-threshold Extrapolation of Dose-Response Curves Is a Challenge for Managing the Risk Associated with Occupational Exposure to Carcinogenic Agents

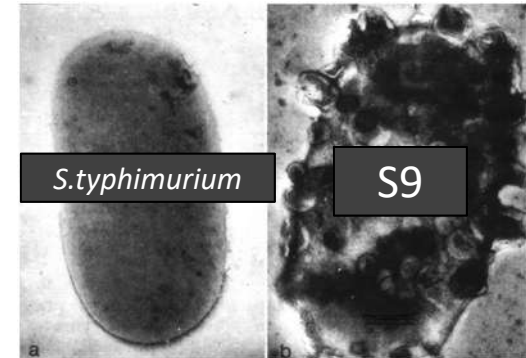
Antonio Mutti

METABOLIC DEACTIVATION OF MUTAGENS

S. De Flora, Nature 271, 455-456, 1978



Test di Ames
Test Salmonella/microsomi



Compound	Amount per plate (µg)	Amount of S-9 fraction per plate (µl)					
		0	10	20	30	40	50
Controls	0	234	241	215	223	218	209
2-Aminofluorene	20	216	325	810	1,430	1,725	2,095
Sodium dichromate	40	705	420	370	283	228	221
Sodium azide	1	645	397	302	251	234	237
Sodium nitrite	5,000	568	454	396	361	358	341
Captan	2	845	570	436	390	327	296
5-Nitro-2-furoic acid	20	1,035	640	529	451	385	337

METABOLIC DEACTIVATION OF MUTAGENS

S. De Flora, Nature 271, 455-456, 1978



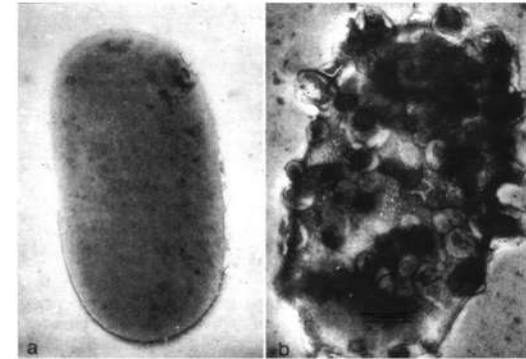
Löfroth, G. The mutagenicity of hexavalent chromium is decreased by microsomal metabolism. *Naturwissenschaften* 65, 207–208 (1978)

This work has been supported by ERDA grant E(04-3)-34-PA156 and carried out in the laboratory of Dr. B.N. Ames, University of California, Berkeley, whom I would like to thank for his support and advice.

Controls	0	234	241	215	223	218	209
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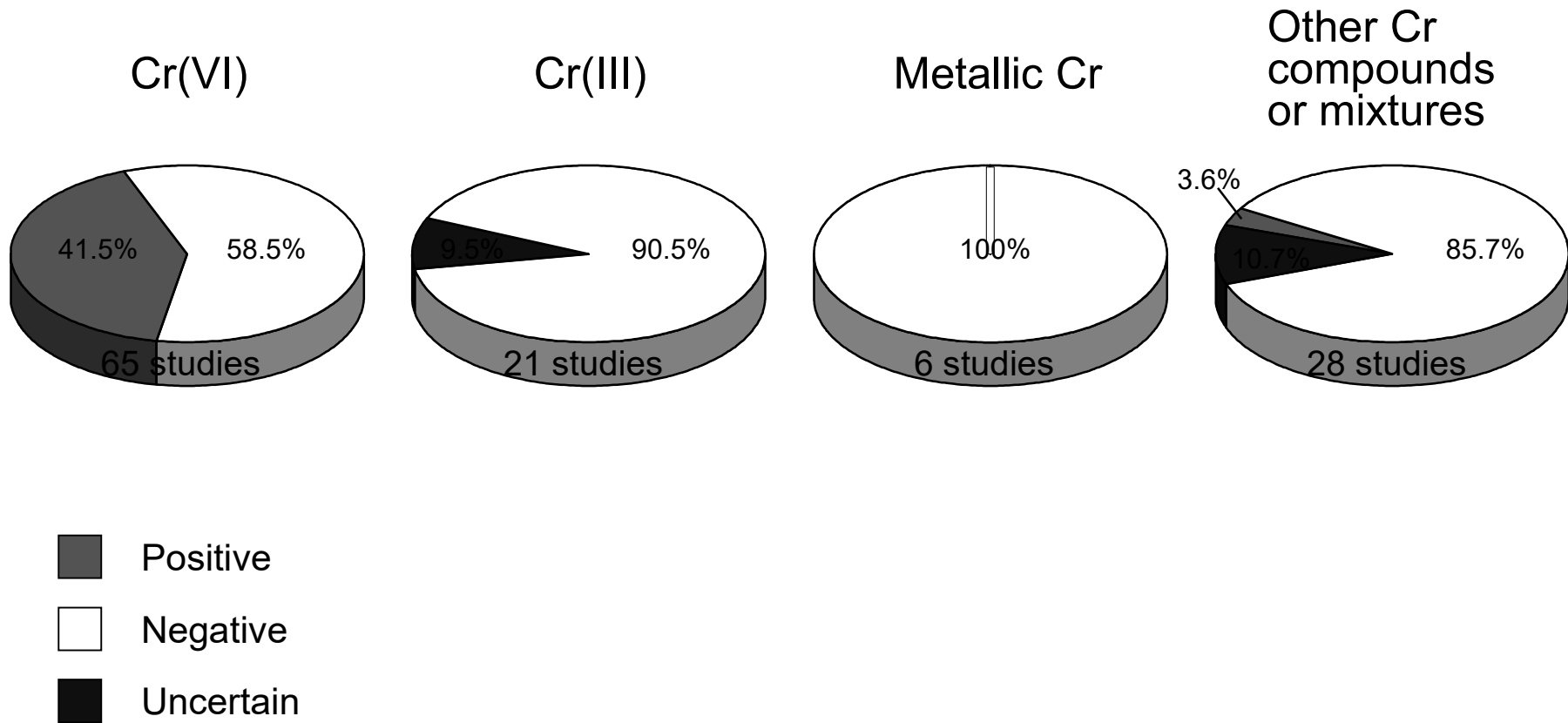
CARCINOGENICITY OF CHROMIUM IN HUMANS

(IARC, Vol. 49, 1990)

There is inadequate evidence for the carcinogenicity of metallic chromium and of Cr(III) compounds (*Group 3*)

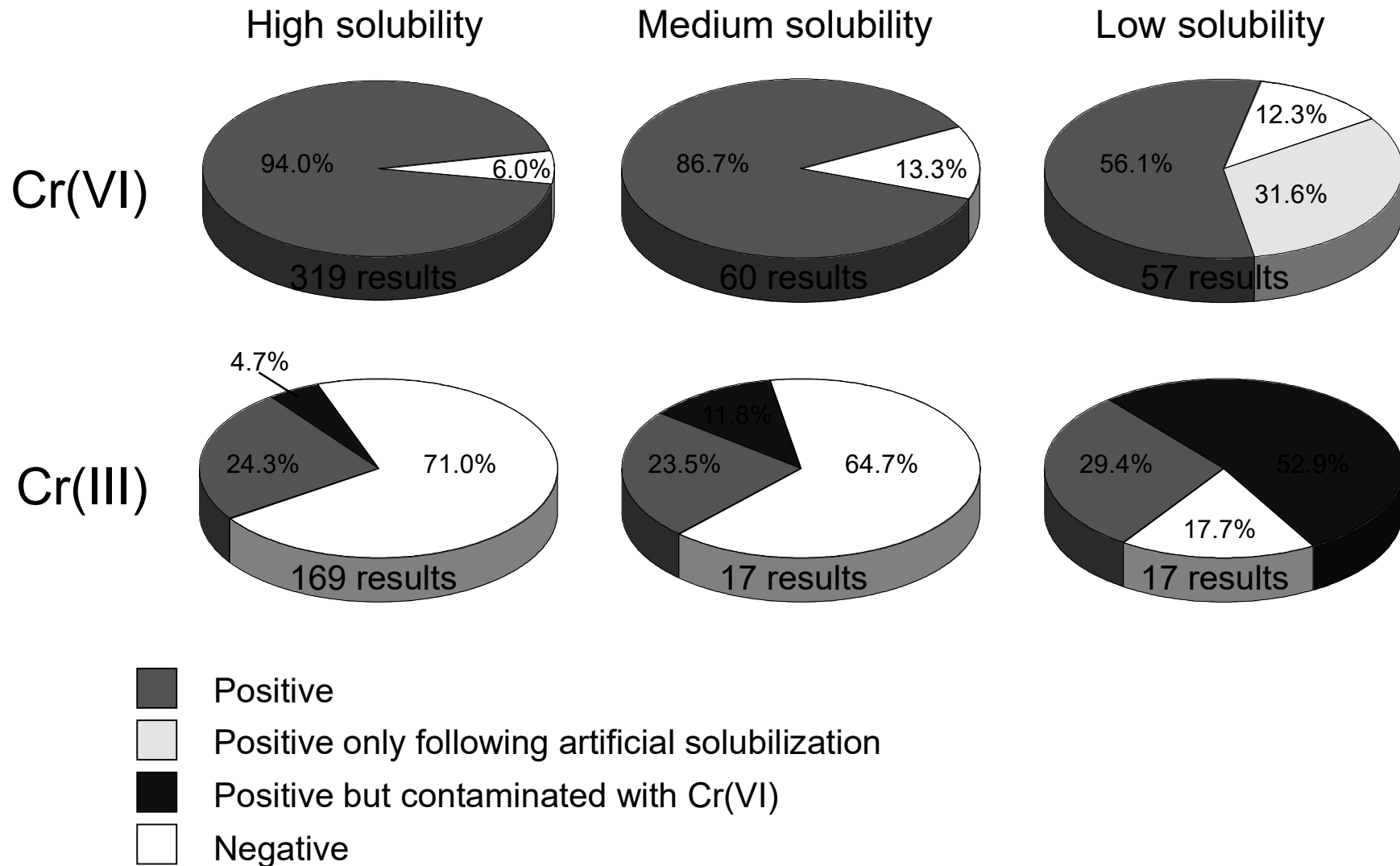
There is sufficient evidence for the carcinogenicity of Cr(VI) compounds (*Group 1*) as encountered in the chromate production, chromate pigment production and chromium plating industries

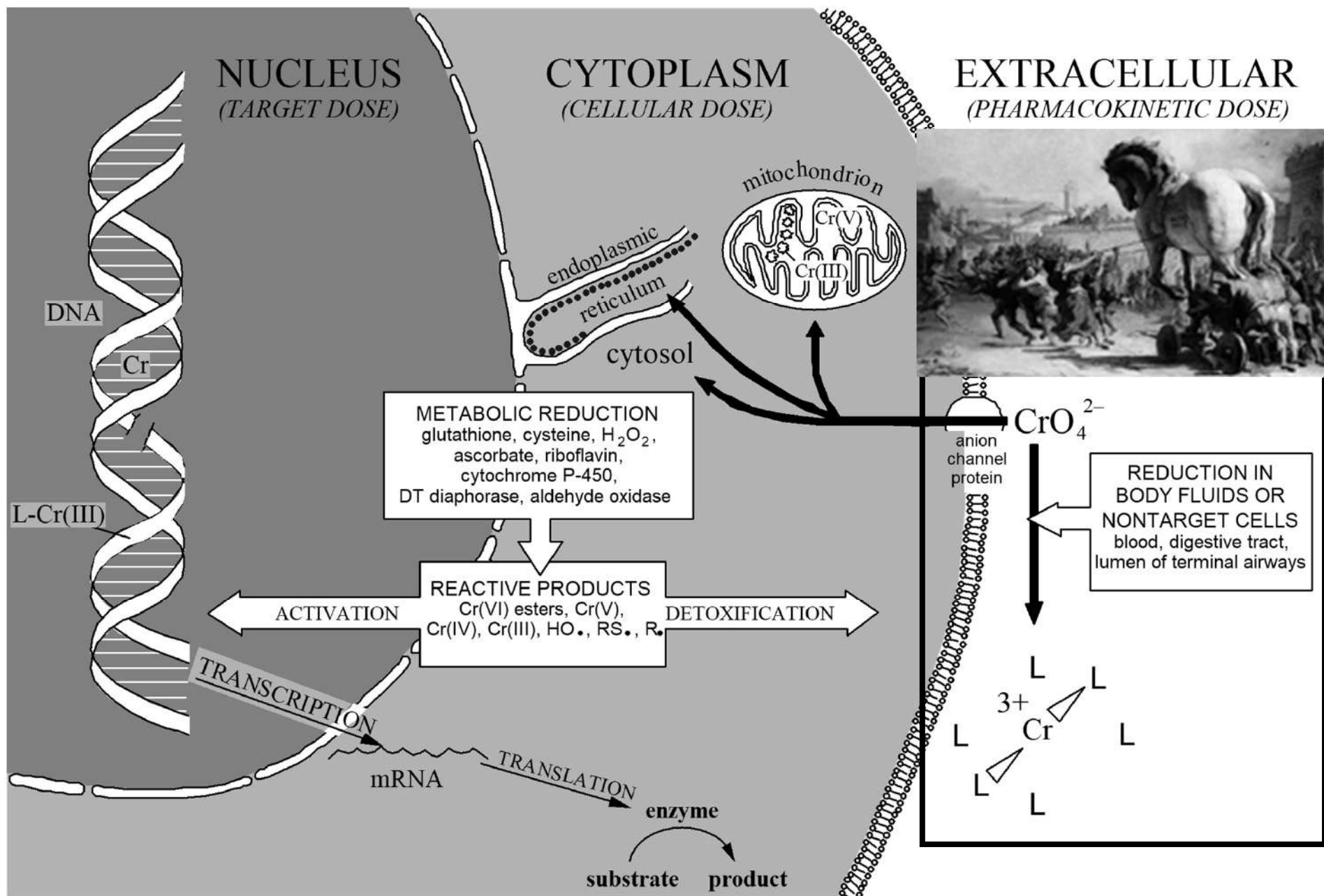
CARCINOGENICITY ASSAYS OF CHROMIUM COMPOUNDS IN RODENTS (IARC, 1990)



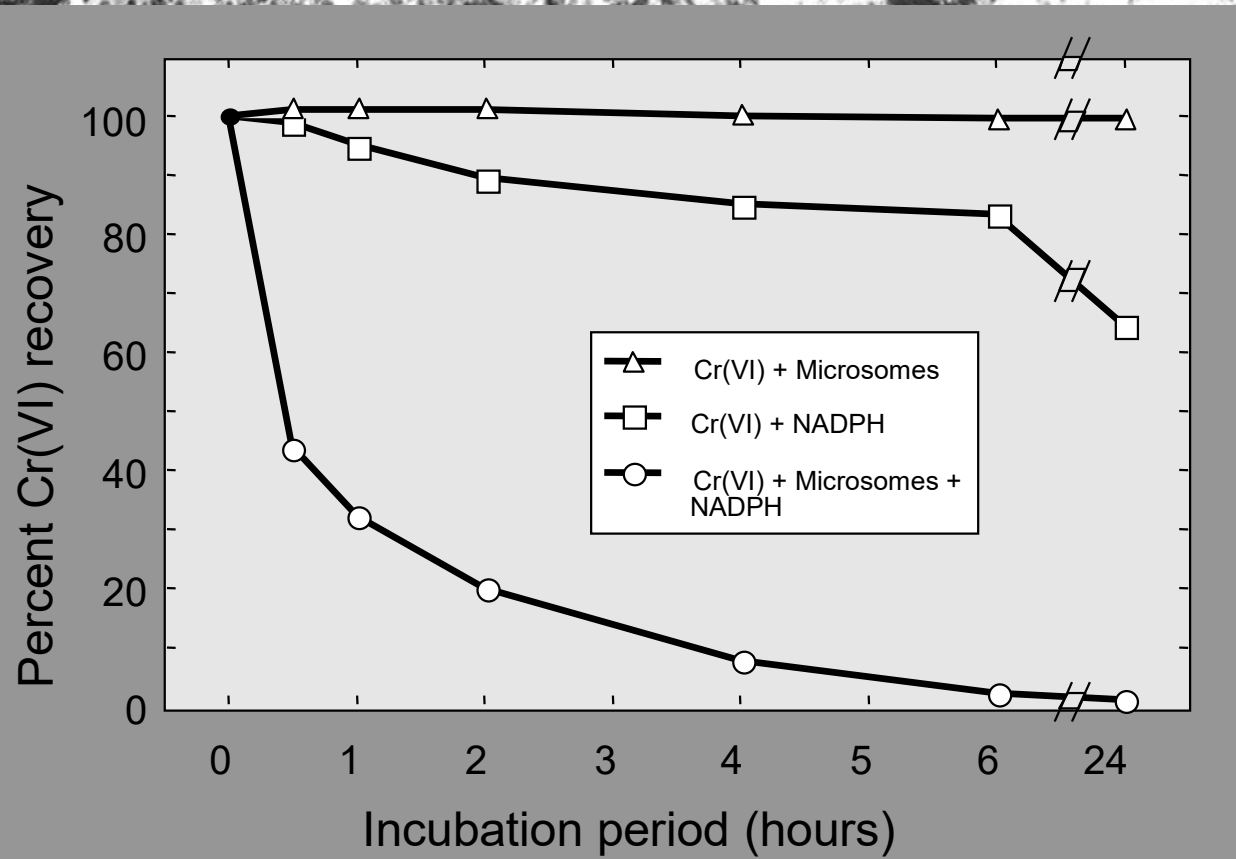
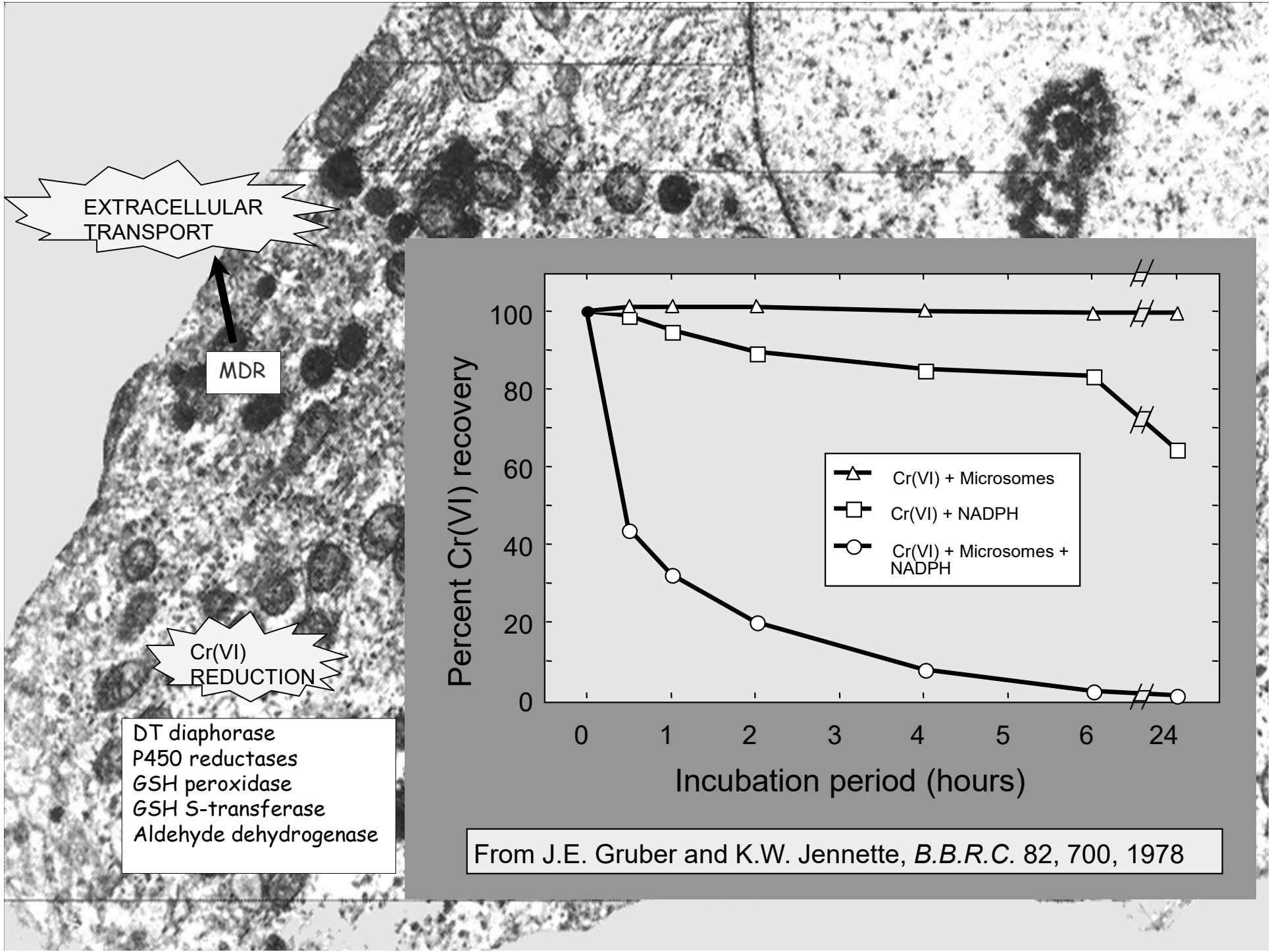
RESULTS OBTAINED WITH CHROMIUM COMPOUNDS IN CELLULAR SYSTEMS (S. De Flora et al., 1990)

700 data relative to 32 chromium compounds tested in 130 experimental test systems

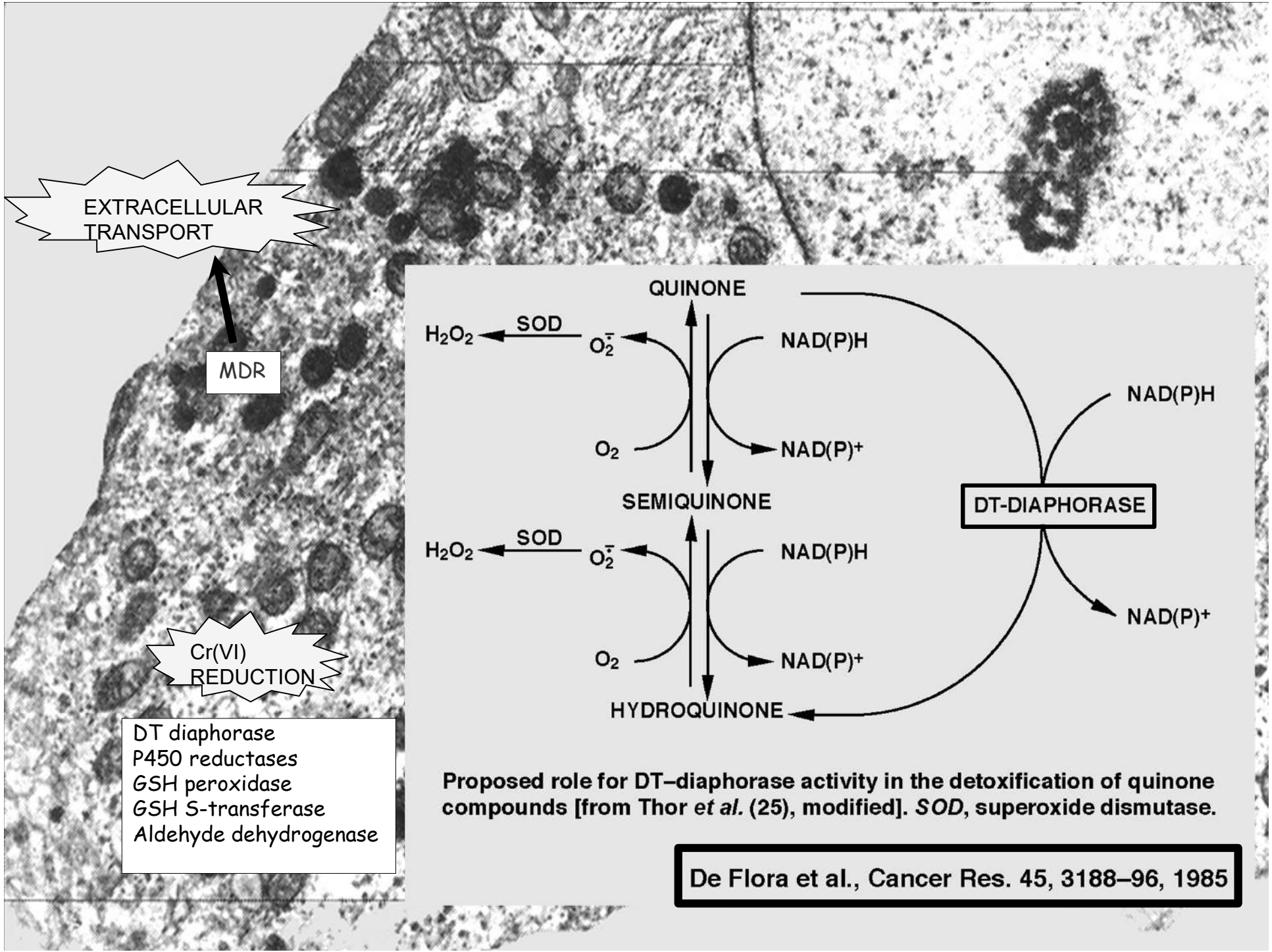




S. De Flora and K.E. Wetterhahn, Life Chem. Rep. 7, 169-244, 1989



From J.E. Gruber and K.W. Jennette, *B.B.R.C.* 82, 700, 1978

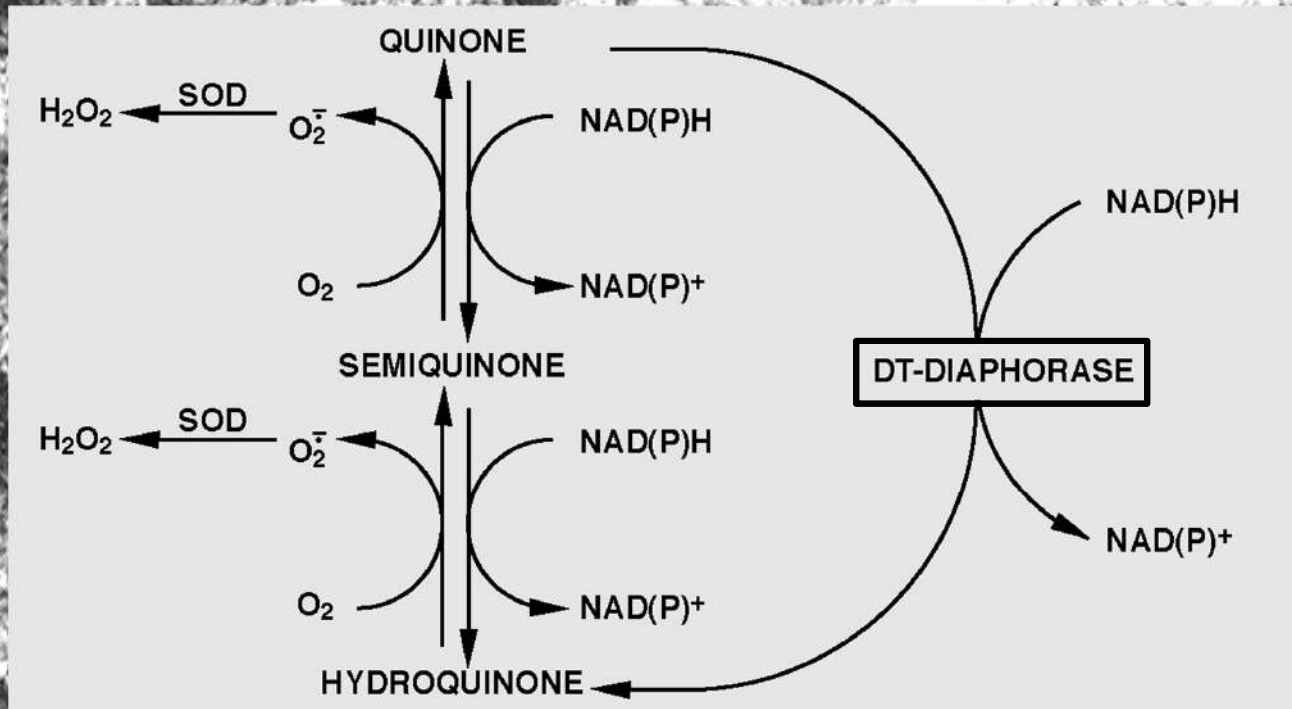


EXTRACELLULAR
TRANSPORT

MDR

Cr(VI)
REDUCTION

DT diaphorase
P450 reductases
GSH peroxidase
GSH S-transferase
Aldehyde dehydrogenase

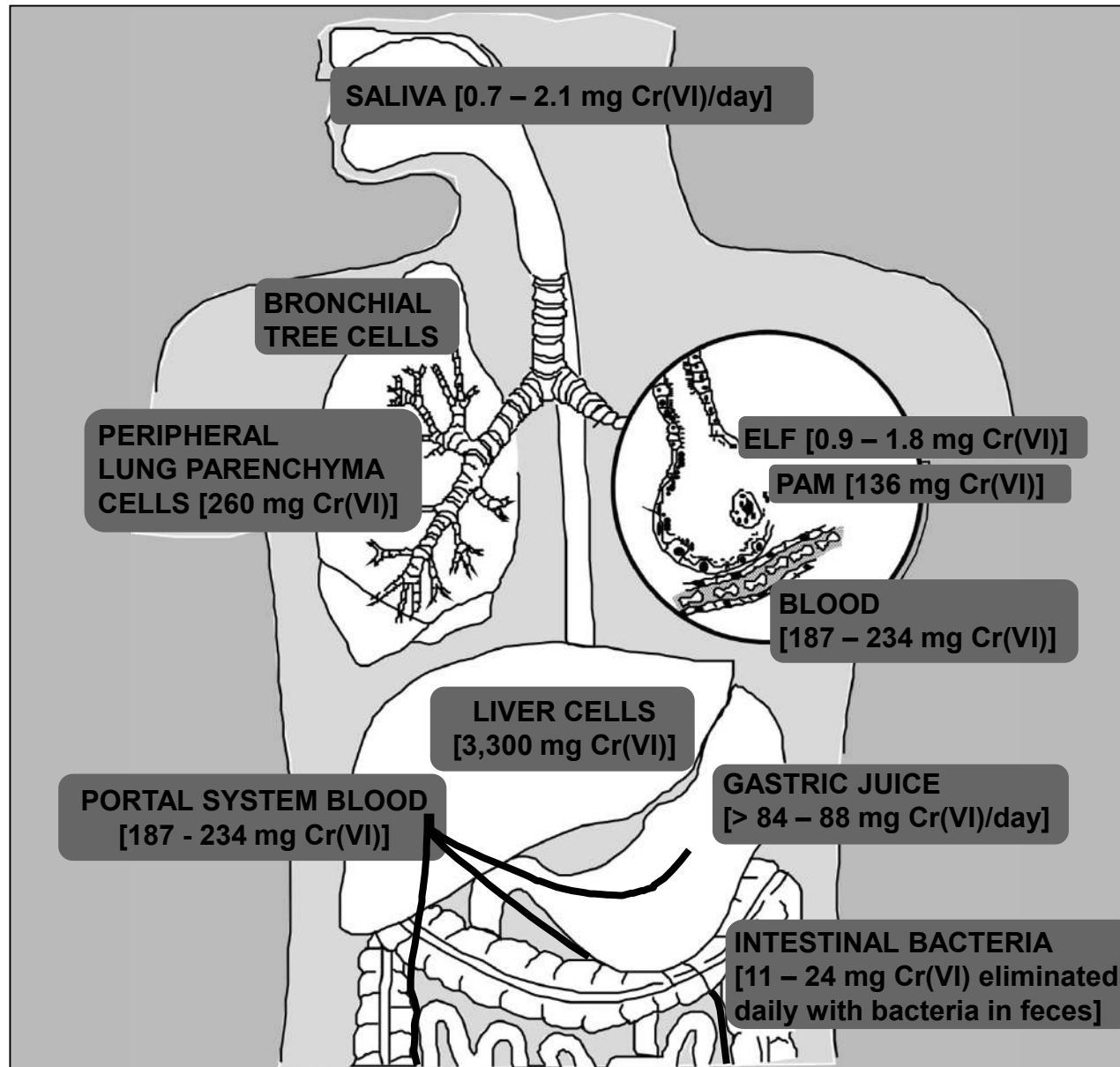


Proposed role for DT-diaphorase activity in the detoxification of quinone compounds [from Thor *et al.* (25), modified]. SOD, superoxide dismutase.

De Flora *et al.*, *Cancer Res.* 45, 3188–96, 1985

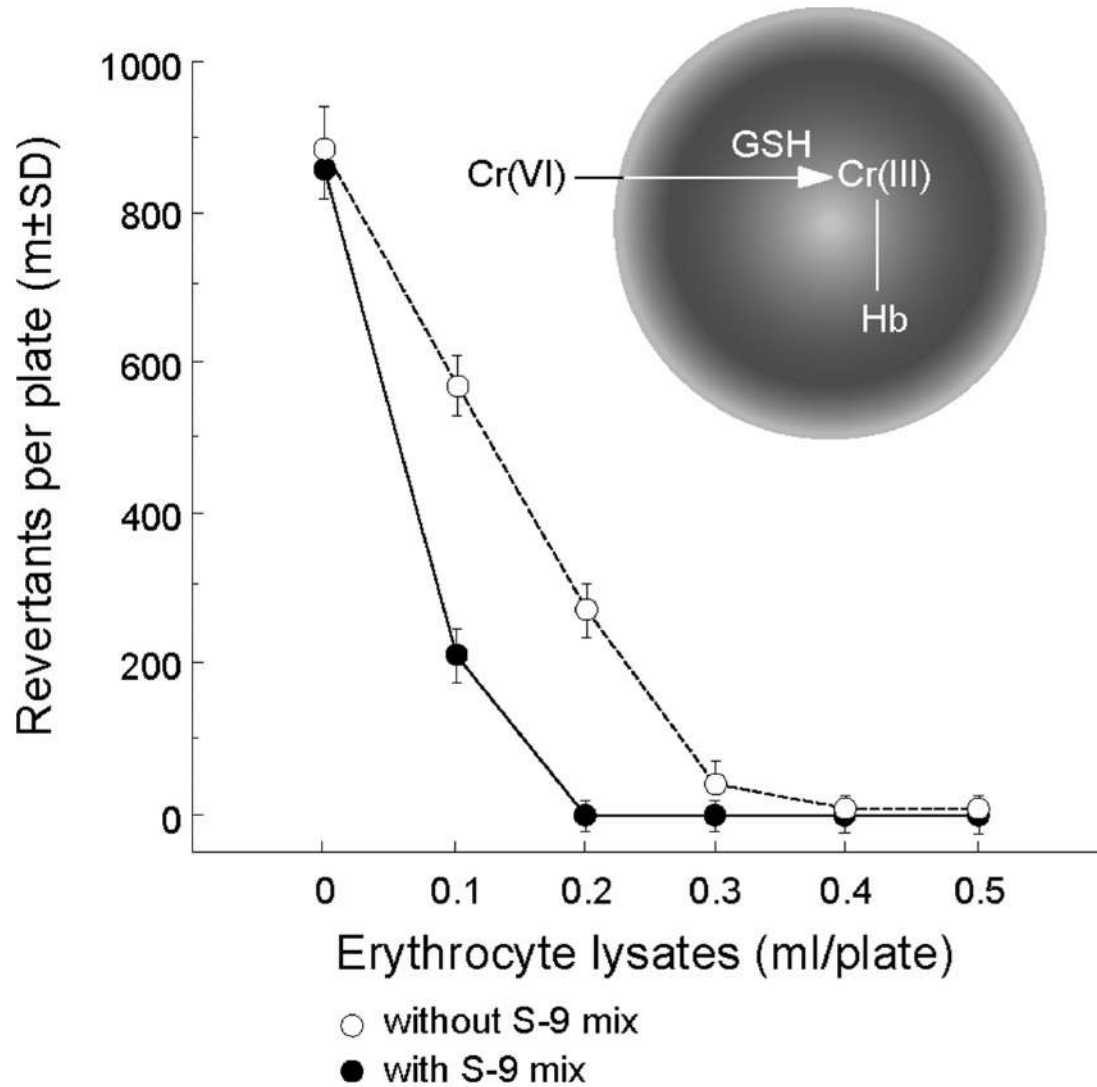
CHROMIUM(VI) REDUCING CAPACITY OF ORGANS, CELL POPULATIONS AND FLUIDS IN THE HUMAN BODY

De Flora et al., Carcinogenesis 18, 531–537, 1997

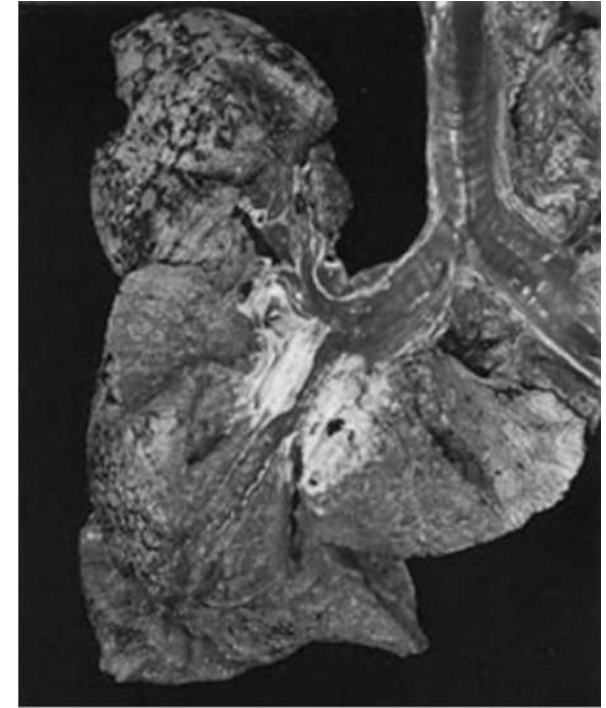


REDUCTION OF Cr(VI) BY HUMAN ERYTHROCYTES

(FL. Petrilli and S. De Flora, *Mutat. Res.* 54,139–147, 1978)

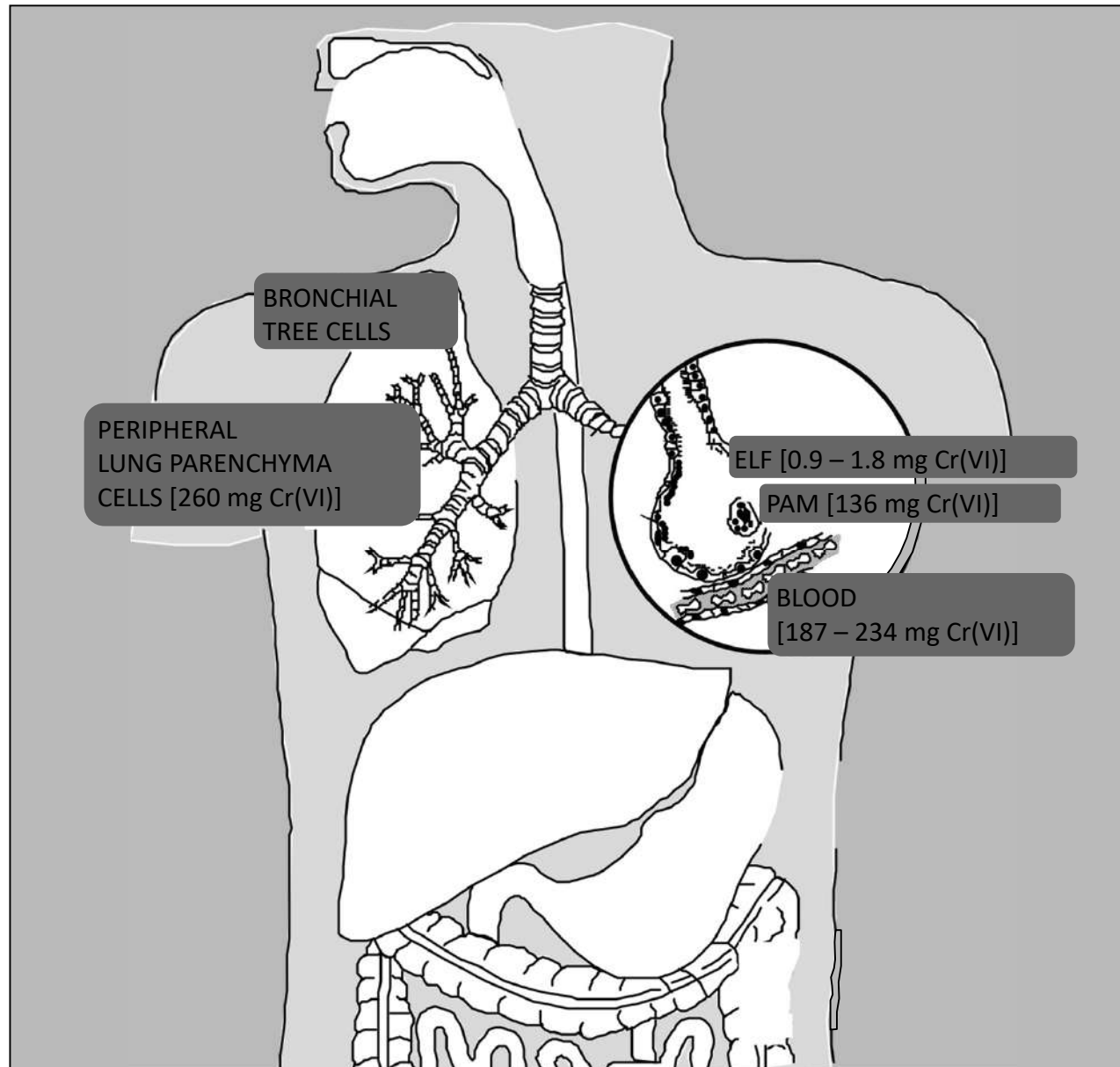


“For cancers other than those of the lungs and sinonasal cavity, no consistent pattern of cancer risk has been demonstrated in those workers exposed to chromium”



- International Agency for Research on Cancer (1990) Vol. 49
- M.D. Cohen et al. (1993) Crit. Rev. Toxicol. 23: 255–281
- R.B. Hayes (1997) Cancer Causes Control 8: 371–385
- ATSDR, U.S. Dept. of Health and Human Services (2000)
- S. De Flora (2000) Carcinogenesis 21: 533-541

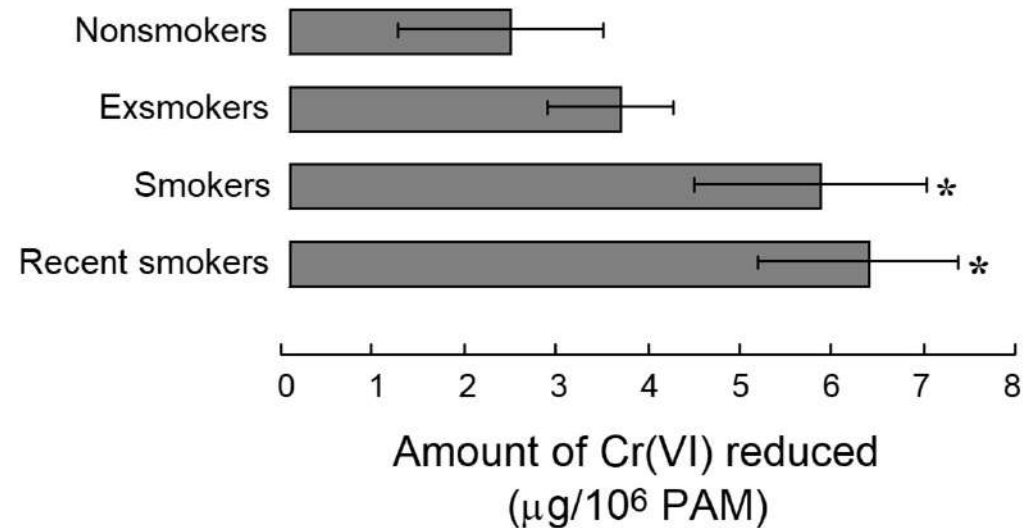
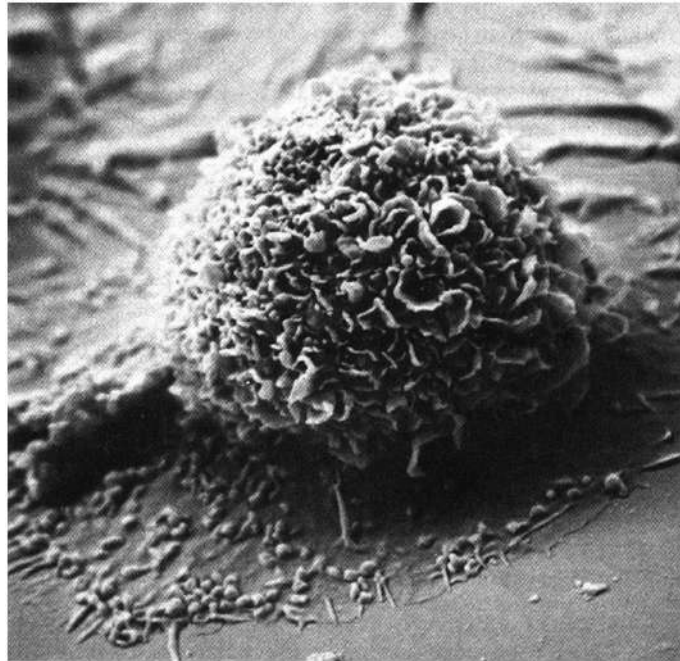
CHROMIUM(VI) REDUCING CAPACITY OF ORGANS, CELL POPULATIONS AND FLUIDS IN THE HUMAN RESPIRATORY TRACT



De Flora et al., Carcinogenesis 18, 531–537, 1997

Cr(VI) REDUCTION BY HUMAN ALVEOLAR MACROPHAGES (PAM)

F L Petrilli, G A Rossi, A Camoirano, M Romano, D Serra, C Bennicelli, A De Flora, S De Flora
J. Clin. Invest. 77, 1917–24, 1986



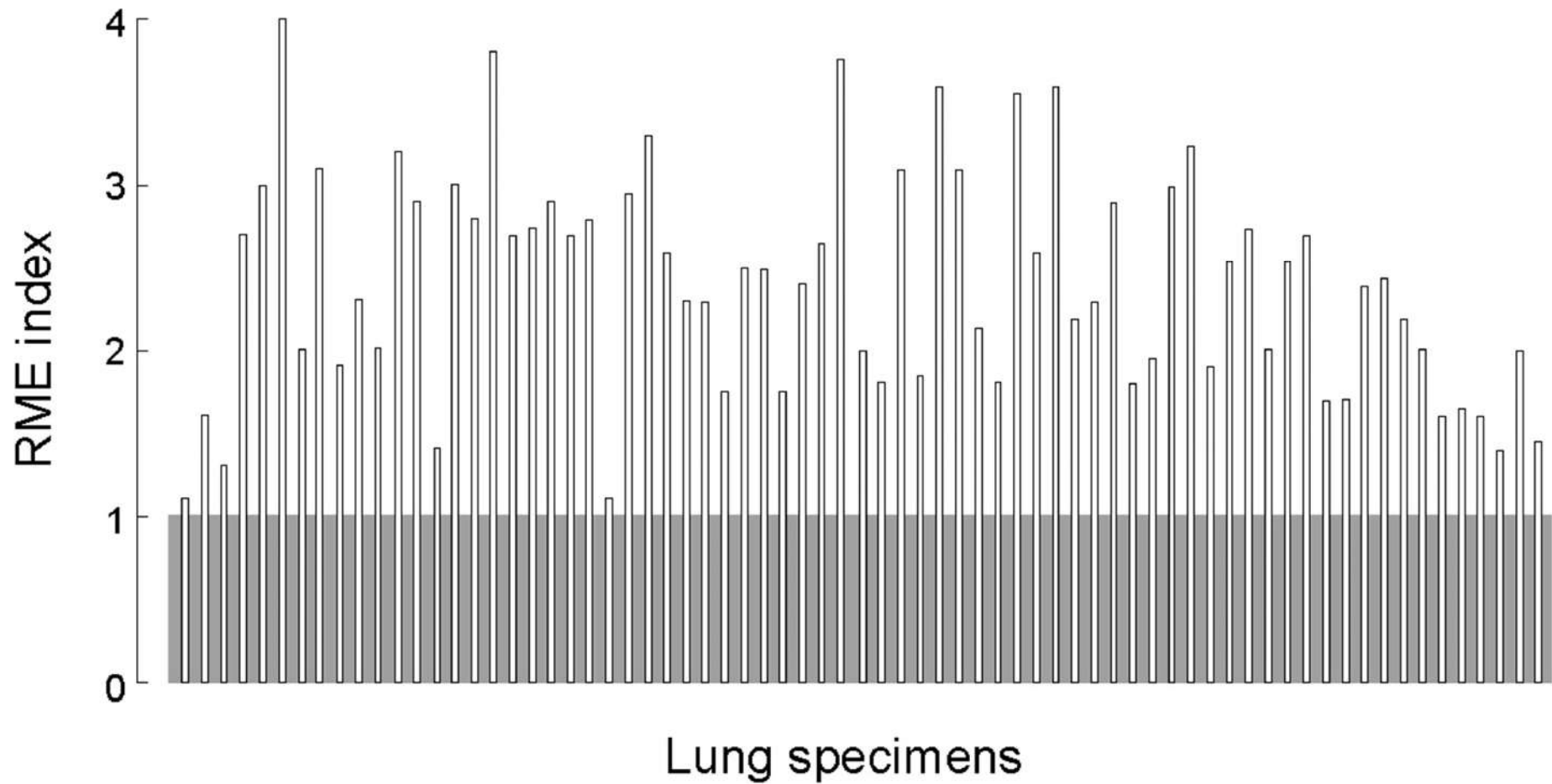
* $P < 0.01$, as compared to nonsmokers and exsmokers

The effect of inhaled **chromium** on different exhaled breath condensate biomarkers among chrome-plating workers. Caglieri A, Goldoni M, Acampa O, Andreoli R, Vettori MV, Corradi M, Apostoli P, Mutti A. Environ Health Perspect. 2006 Apr;114(4):542-6.

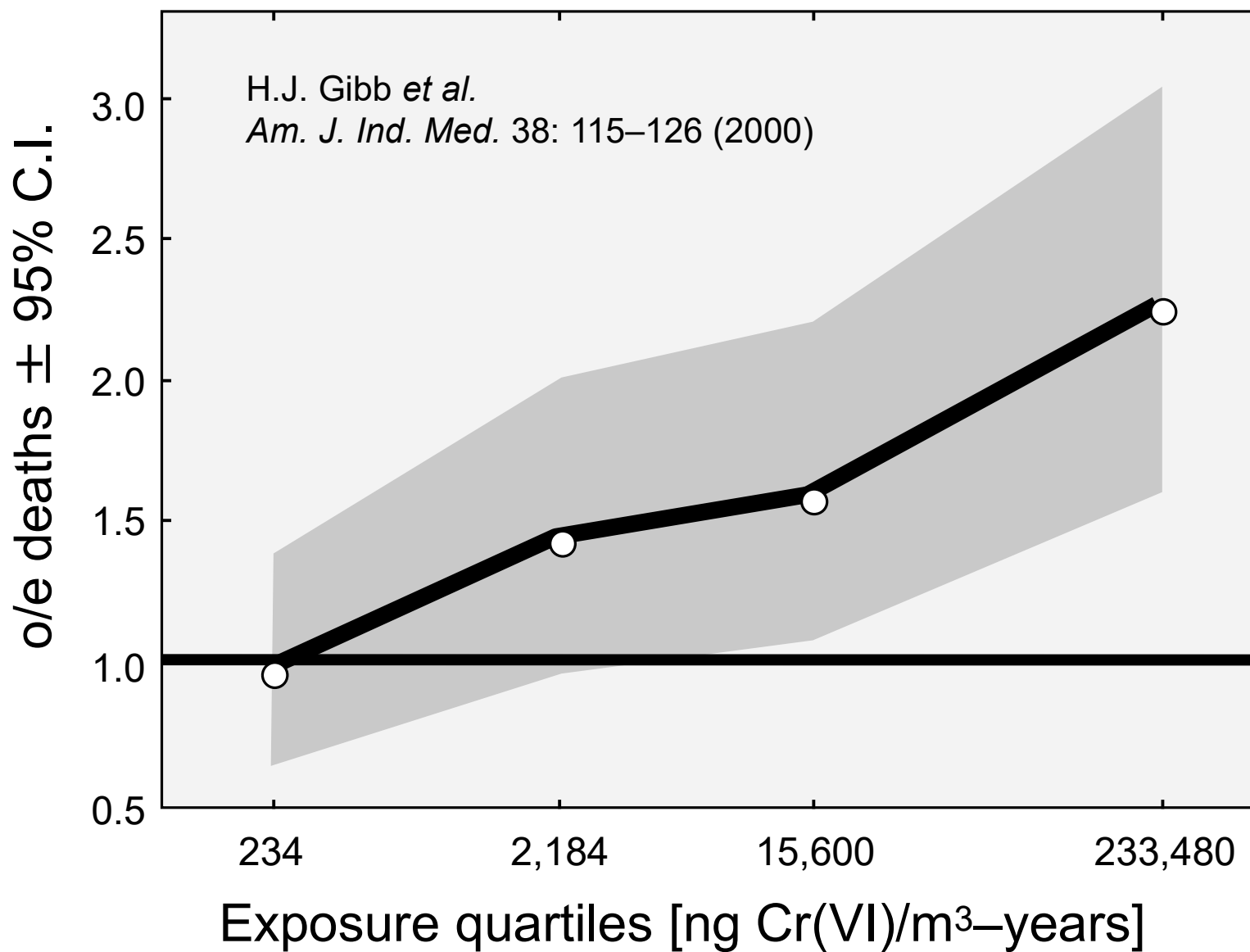
Cr(VI) REDUCTION BY HUMAN LUNG PARENCHYMA PREPARATIONS

S De Flora, S Petruzzelli, A Camoirano, C Bennicelli, M Romano, M Rindi, L Ghelarducci, C Giuntini

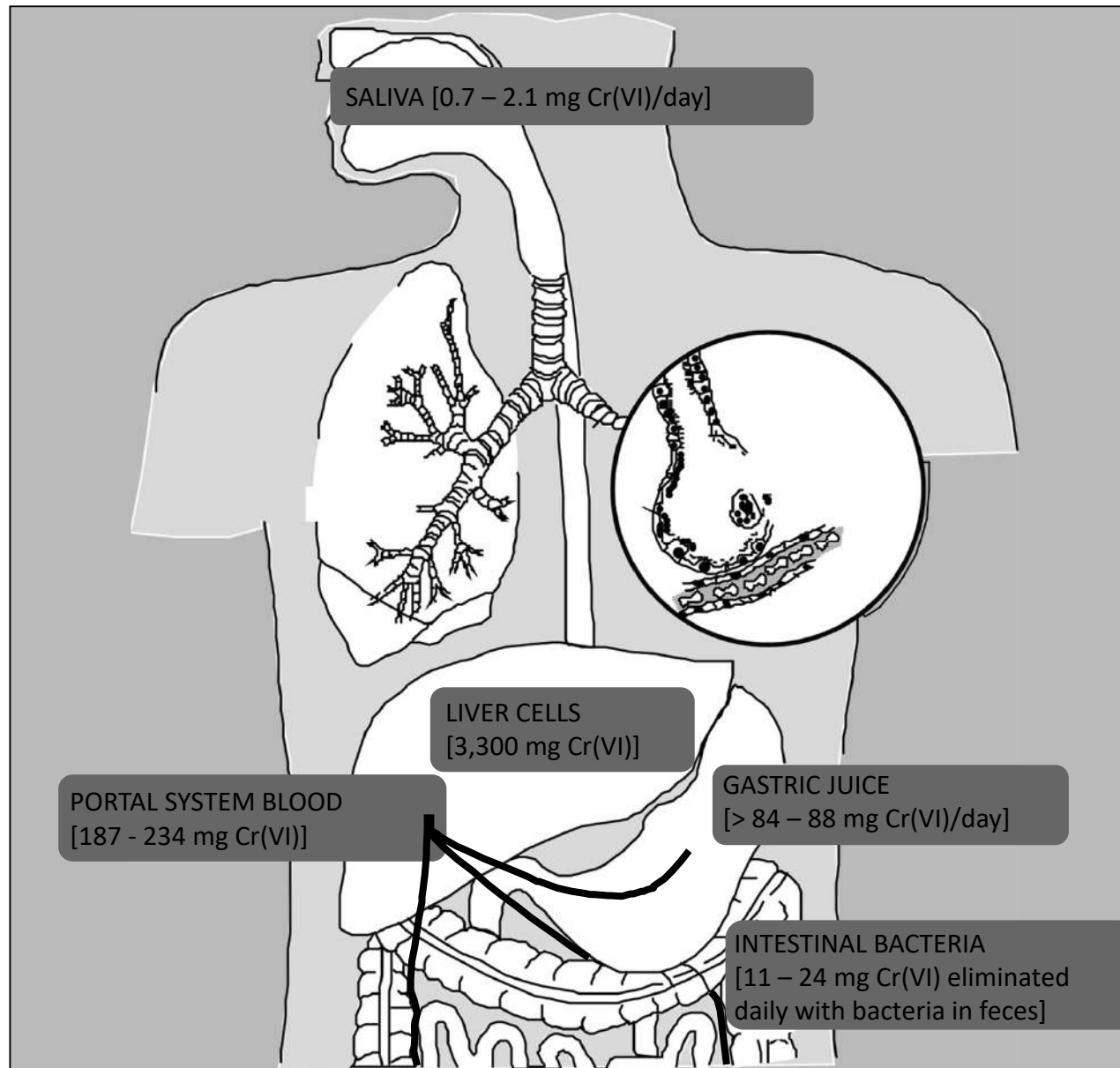
Cancer Res. 47, 4740–45, 1987



LUNG CANCER DEATHS IN CHROMATE PRODUCTION WORKERS



CHROMIUM(VI) REDUCING CAPACITY OF ORGANS, CELL POPULATIONS AND FLUIDS IN THE HUMAN DIGESTIVE SYSTEM

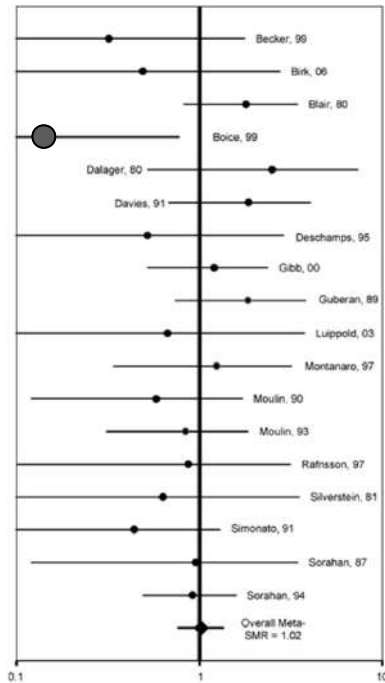


De Flora et al., Carcinogenesis 18, 531–537, 1997

OCCUPATIONAL EXPOSURE TO Cr(VI) AND GASTROINTESTINAL CANCERS: A META-ANALYSIS

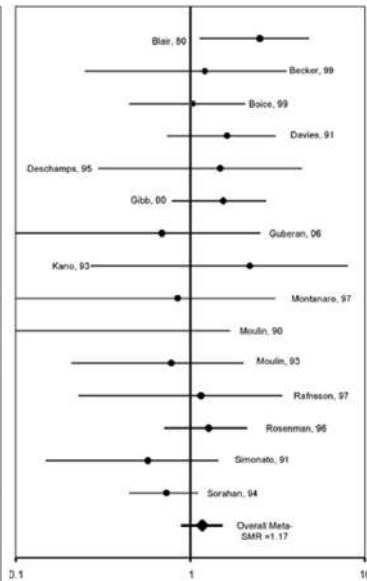
N.M. Gatto et al., Cancer Epidemiol. 34, 388–399, 2010

ORAL



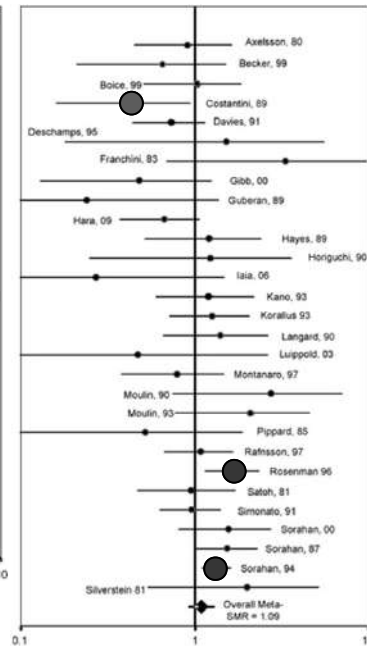
17 studies
Meta-SMR = 1.02

ESOPHAGEAL



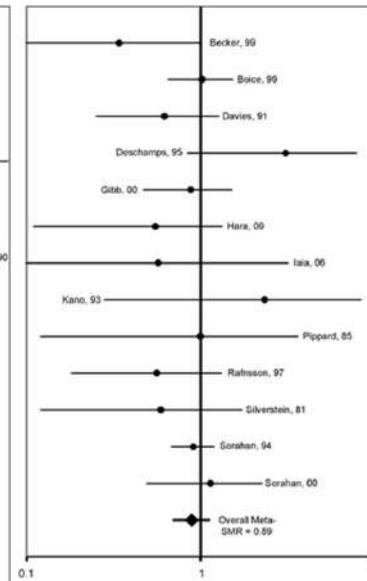
15 studies
Meta-SMR = 1.17

STOMACH



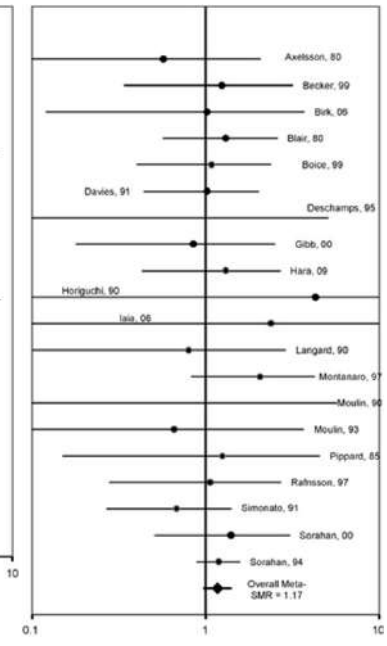
29 studies
Meta-SMR = 1.09

COLON



13 studies
Meta-SMR = 0.89

RECTAL

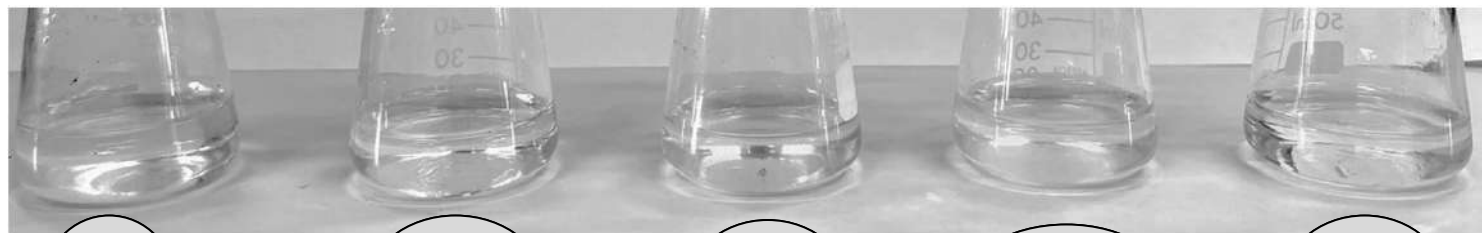
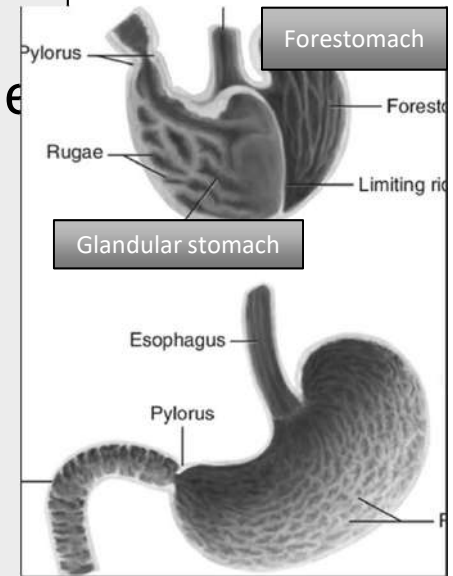


20 studies
Meta-SMR = 1.17

NTP (2008): 2-Year drinking water study of sodium dichromate dihydrate in male and female B6C3F1 mice and F344 rats

Significant increase of the incidence of squamous cell epithelium tumours of the oral mucosa or tongue in the high-dose groups (516 mg/l) of both male and female rats

Significant increase of the incidence of tumours of the small intestine (duodenum, jejunum, or ileum) in the two highest dose groups of male mice (85.7 and 257.4 mg/l) and female mice (172 and 516 mg/l)



0

85.7

172

257.4

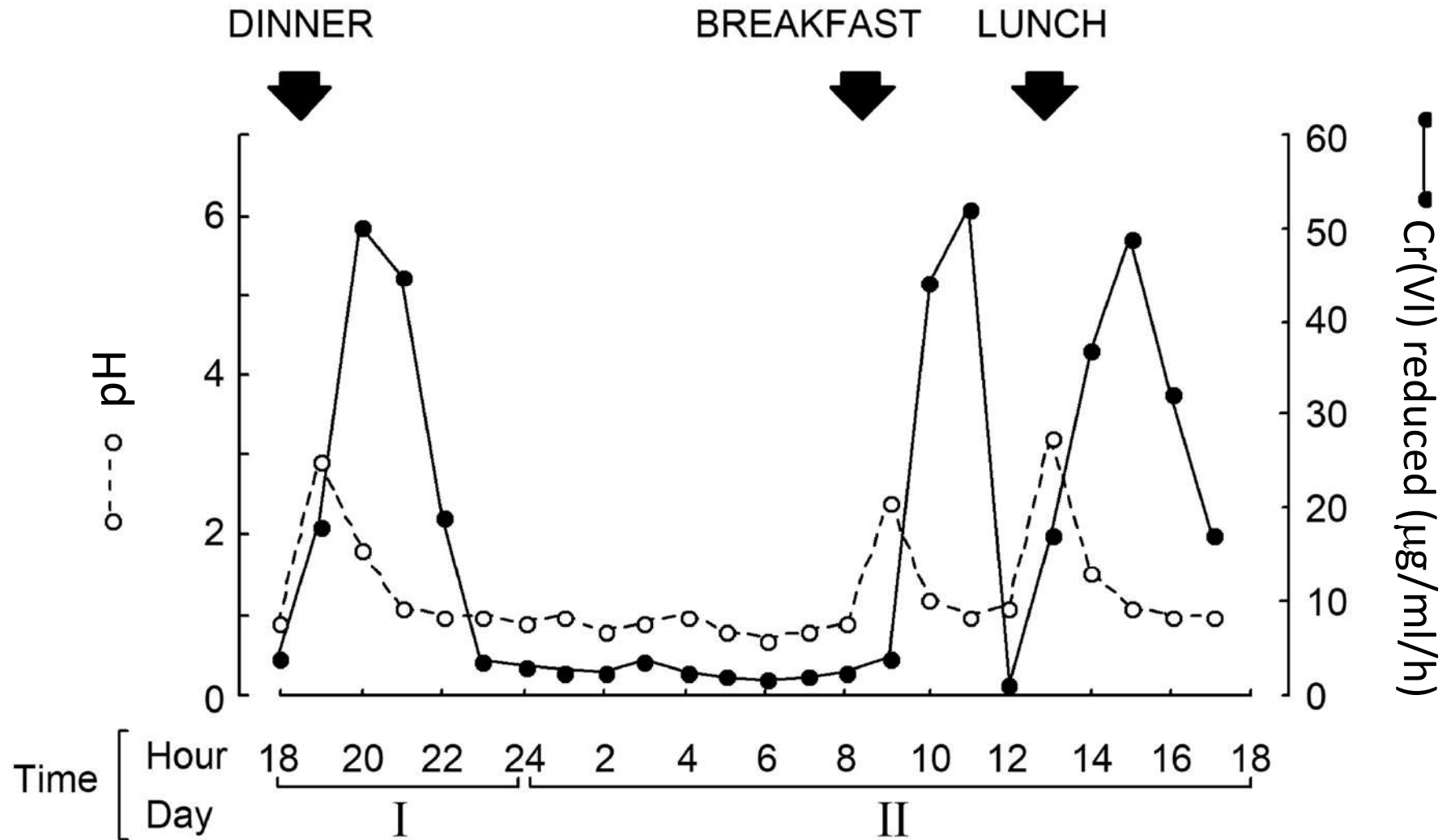
516

mg/l

CIRCADIAN REDUCTION OF Cr(VI) BY HUMAN GASTRIC JUICE

De Flora S, Badolati GS, Serra D, Picciotto A, Magnolia MR, Savarino V

Mutat. Res. 192, 169–174, 1987

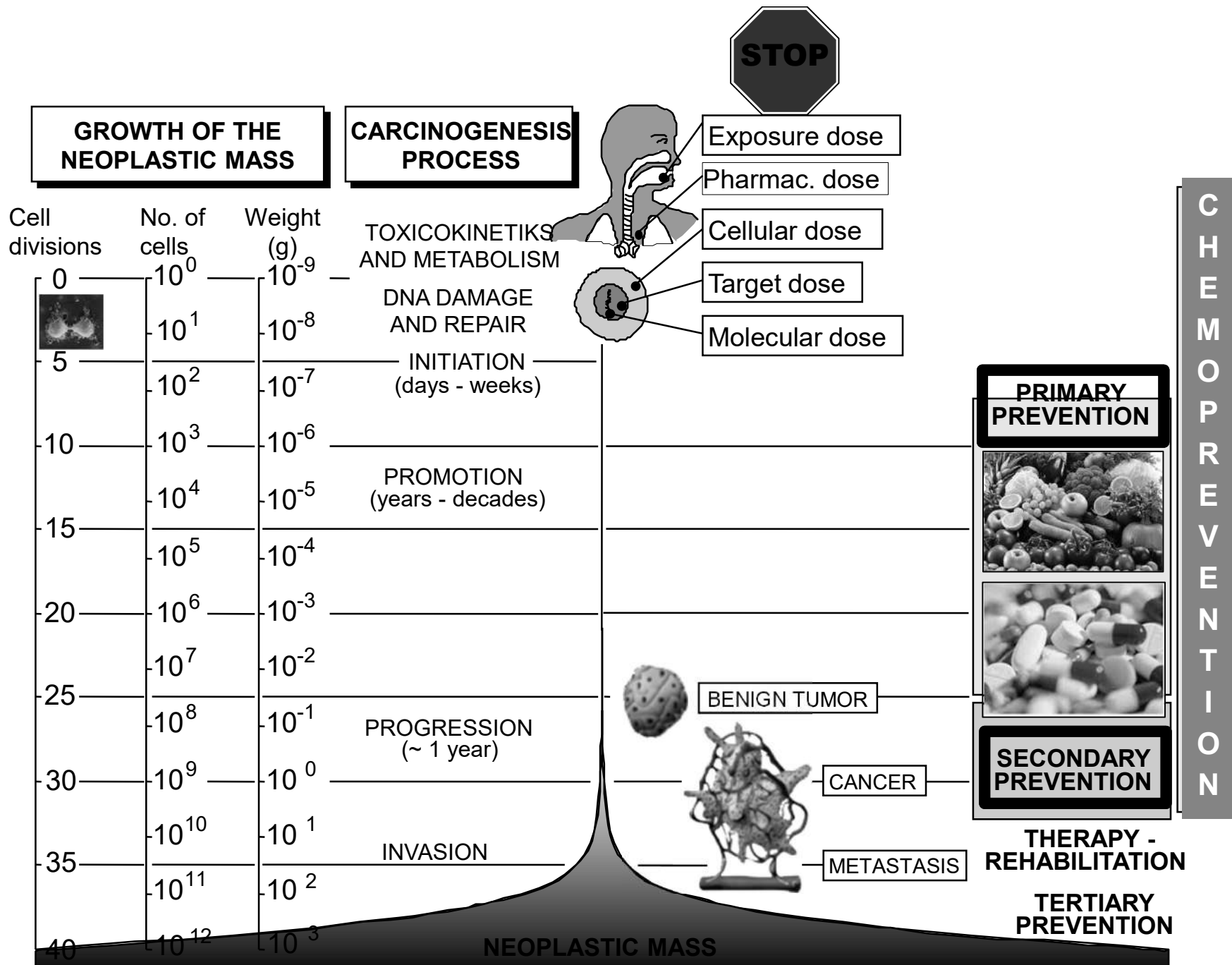


METABOLIC MECHANISMS AND Cr(VI) DETOXIFICATION

The IARC Working Group (1990) “interpreted these findings as indicating mechanisms that limit the activity of Cr(VI) compounds *in vivo*”

The U.S. Environmental Protection Agency (1991) concluded that “the body’s normal physiology provides detoxification for Cr(VI)”

The U.S. Department of Health and Human Services (2000) indicated that these “mechanisms limit the bioavailability and attenuate the potential effects of Cr(VI) compounds *in vivo*”



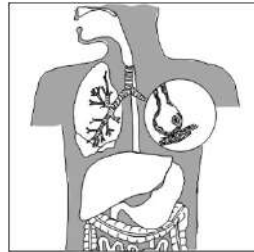
MECHANISMS OF CANCER CHEMOPREVENTIVE AGENTS

S. De Flora and C. Ramel, *Mutat. Res.*, 202, 285–306, 1988

PRIMARY PREVENTION

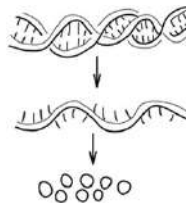
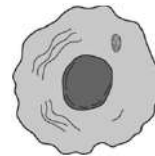
1. Inhibition of mutation and cancer initiation in the extracellular environment or in nontarget cells

- 1.1. Inhibition of uptake of mutagens/carcinogens
 - 1.1.1. Inhibition of penetration
 - 1.1.2. Removal from the organism
- 1.2. Inhibition of the endogenous formation of mutagens and carcinogens
 - 1.2.1. Inhibition of the nitrosation reaction
 - 1.2.2. Modification of the intestinal microbial flora
- 1.3. Complexation, dilution and/or deactivation of mutagens/carcinogens outside cells
 - 1.3.1. By physical or mechanical means
 - 1.3.2. By chemical reaction
 - 1.3.3. By enzyme-catalyzed reaction
- 1.4. Favoring absorption of protective agents
- 1.5. Stimulation of trapping and detoxification in nontarget cells



2. Inhibition of mutation and cancer initiation in target cells

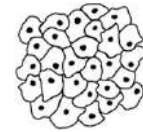
- 2.1. Modification of transmembrane transport
 - 2.1.1. Inhibition of cellular uptake
 - 2.1.2. Stimulation of extrusion outside cells
- 2.2. Modulation of metabolism
 - 2.2.1. Inhibition of activation of promutagens/ procarcinogens by Phase I enzymes
 - 2.2.2. Induction of Phase I detoxification and Phase II conjugation pathways, or acceleration of decomposition of reactive metabolites
 - 2.2.3. Stimulation of activation, coordinated with detoxification and blocking of reactive metabolites
- 2.3. Blocking or competition
 - 2.3.1. Trapping of electrophiles by either chemical reaction or enzyme-catalyzed conjugation
 - 2.3.2. Antioxidant activity and scavenging of reactive species
 - 2.3.3. Protection of DNA nucleophilic sites
- 2.4. Inhibition of cell replication
- 2.5. Maintenance of DNA structure and modulation of DNA metabolism and repair
 - 2.5.1. Increase of fidelity of DNA replication and repair
 - 2.5.2. Stimulation of repair and/or reversion of DNA damage
 - 2.5.3. Inhibition of error-prone repair pathways
 - 2.5.4. Correction of hypomethylation
 - 2.5.5. Inhibition of histone deacetylation
 - 2.5.6. Blocking of telomerases or inhibition of their activity
- 2.6. Control of gene expression
 - 2.6.1. Targeted inactivation of oncogenes
 - 2.6.2. Inhibition of oncogene expression
 - 2.6.3. Inhibition of oncogene sequences or activity
 - 2.6.3.1. Inhibition of translation targeted to oncogene mRNA
 - 2.6.3.2. Inhibition of transcription of specific DNA sequences
 - 2.6.3.3. Blocking of target genes
 - 2.6.3.4. Farnesyltransferase inhibition
 - 2.6.4. Neutralization or post-translational modification of oncogene products
 - 2.6.5. Replacement of deleted tumor suppressor genes
 - 2.6.6. Mimicking the DNA binding of tumor suppressor genes by antiidiotypic antibodies
 - 2.6.7. Killing of cells lacking tumor suppressor genes



S. De Flora and L.R. Ferguson, *Mutat. Res.*, 591, 8–15, 2005

3. Inhibition of tumor promotion

- 3.1. Inhibition of genotoxic effects (see 1 and 2)
- 3.2. Antioxidant activity and scavenging of free radicals
- 3.3. Antiinflammatory activity
 - 3.3.1. Cyclooxygenase inhibition
 - 3.3.2. Lipoxygenase inhibition
 - 3.3.3. Inhibition of inducible nitric oxide synthase
 - 3.3.4. Leukotriene receptor antagonism
- 3.4. Inhibition of proteases
- 3.5. Inhibition of cell proliferation
 - 3.5.1. Inhibition of ornithine decarboxylase
 - 3.5.2. Promoting proteasomal degradation of cyclins
 - 3.5.3. Interference with multiple signaling pathways
- 3.6. Induction of cell differentiation
- 3.7. Modulation of cell apoptosis
- 3.8. Signal transduction modulation
- 3.9. Protection of intercellular communications



SECONDARY PREVENTION

4. Inhibition of tumor progression

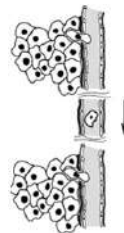
- 4.1. Inhibition of genotoxic effects (see 1 and 2)
- 4.2. Antioxidant activity and scavenging of free radicals
- 4.3. Inhibition of proteases
- 4.4. Signal transduction modulation
- 4.5. Effects on the hormonal status
 - 4.5.1. Selective estrogen receptor modulation
 - 4.5.2. Aromatase inhibition
 - 4.5.3. Selective blocking of prostaglandin E2 receptors
 - 4.5.4. Decrease in ovarian hormones by dietary isoflavones
 - 4.5.5. Inhibiting the pituitary secretion of luteinizing hormone
 - 4.5.6. Preventing conversion of testosterone into dehydrotestosterone by 5 α -reductase
 - 4.5.7. Selective androgen receptor antagonism
- 4.6. Effects on the immune system
- 4.7. Inhibition of angiogenesis
- 4.8. Antineoplastic activity by either mechanical, physical, chemical, or biological means



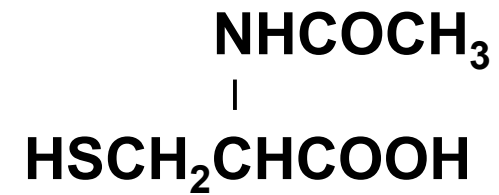
TERTIARY PREVENTION

5. Inhibition of invasion and metastasis

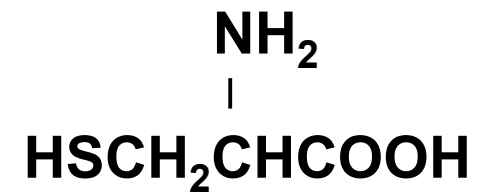
- 5.1. Antioxidant activity and scavenging of free radicals
- 5.2. Signal transduction modulation
- 5.3. Inhibition of cell proliferation (see 3.4)
- 5.4. Modulation of cell apoptosis
- 5.5. Induction of cell differentiation
- 5.6. Inhibition of angiogenesis
- 5.7. Effect on cell-adhesion molecules
- 5.8. Inhibition of proteases involved in basement membrane degradation and modulation of the interaction with the extracellular matrix
- 5.9. Activation of antimetastasis genes



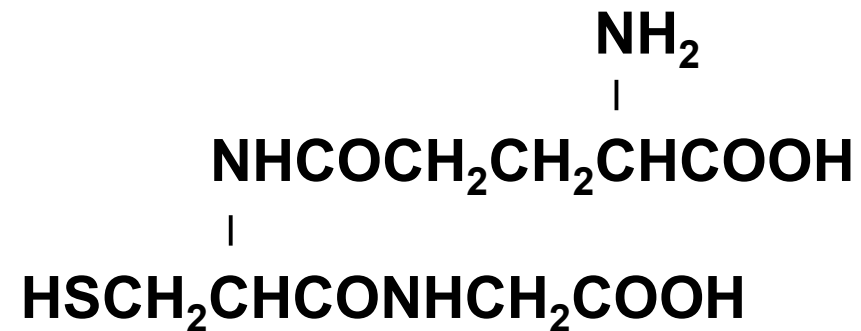
***N*-Acetyl-L-cysteine (NAC)**



L-Cysteine

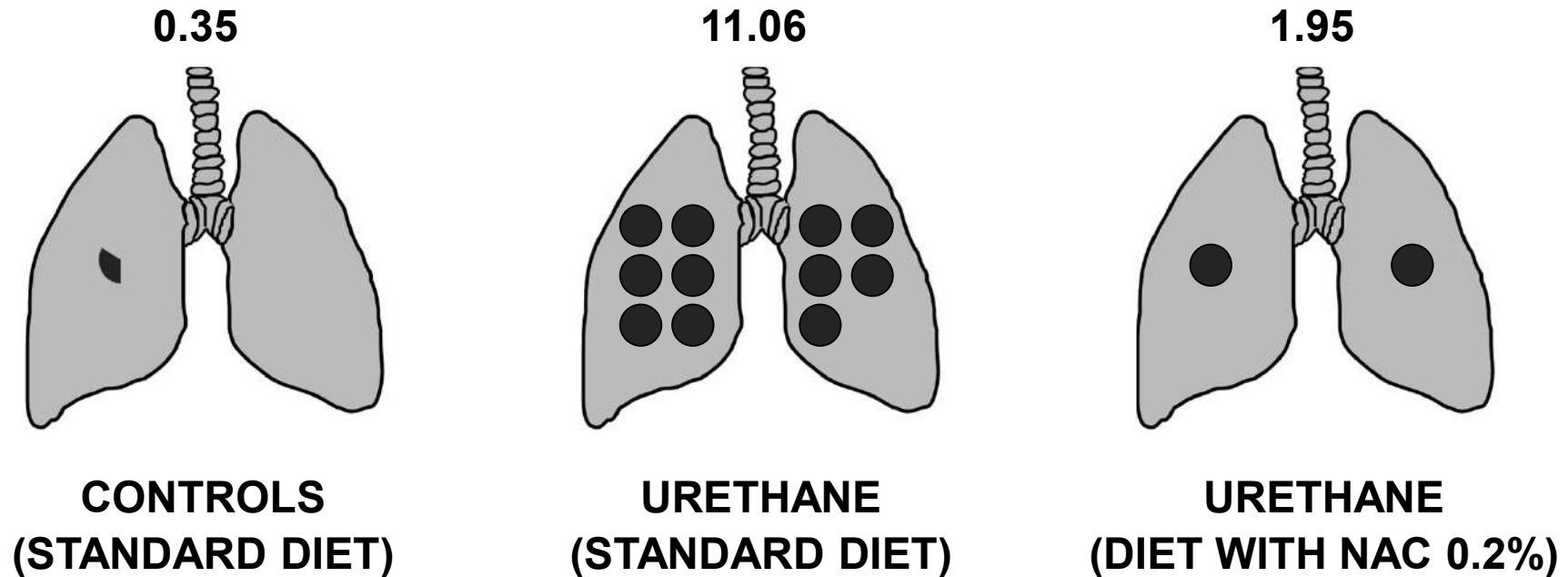


GSH



PREVENTION OF LUNG TUMORS IN MICE

NUMBER OF TUMORS/MOUSE



De Flora S, Astengo M, Serra D, Bennicelli C, Cancer Lett. 32, 235-241, 1986

PASSIVE SMOKING IN MUTANT MICE



P53

S. De Flora *et al.* Molecular alterations and lung tumors in *P53* mutant mice exposed to cigarette smoke. *Cancer Res.* 63, 793–800, 2003

A. Izzotti *et al.* Gene expression in the lung of *P53* mutant mice exposed to cigarette smoke. *Cancer Res.* 64, 8566–72, 2004

Fhit

F. D'Agostini *et al.* Early loss of *Fhit* in the respiratory tract of rodents exposed to environmental smoke. *Cancer Res.* 66, 3936–41, 2006

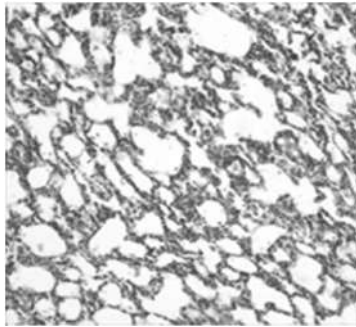
S. De Flora *et al.* Molecular alterations induced by cigarette smoke in mice heterozygous for *Fhit*. *Cancer Res.* 67, 1001–6, 2007

R. Balansky *et al.* Influence of *Fhit* on benzo(a)pyrene induced tumors and alopecia in mice. *PNAS* 103, 7823–8, 2006

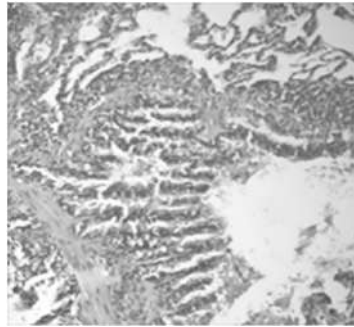
Potent carcinogenicity of cigarette smoke in mice
exposed early in life.

**Balansky R, Ganchev G, Ilcheva M, Steele VE,
D'Agostini F, De Flora S.**

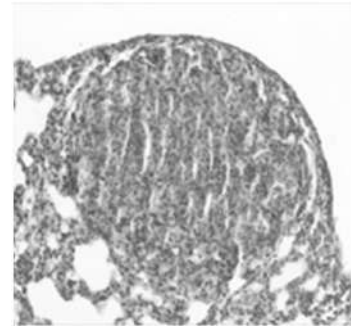
Carcinogenesis. 2007 Oct;28(10):2236-43.



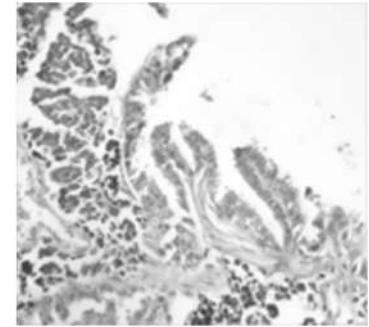
**Hyperplasia of
alveolar epithelium**



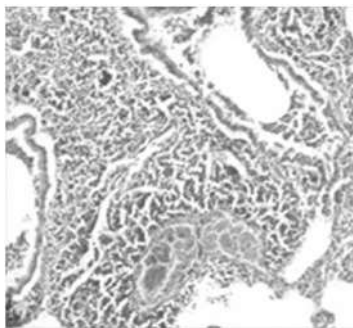
**Papillary hyperplasia
of bronchial epithelium**



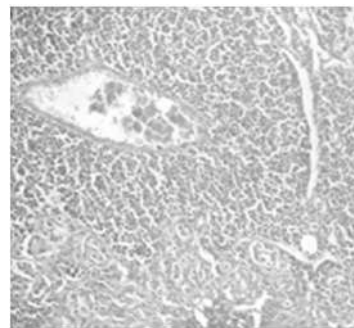
Adenoma



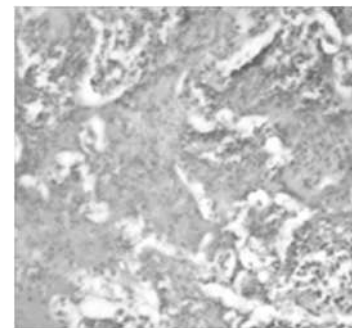
Carcinoma *in situ*



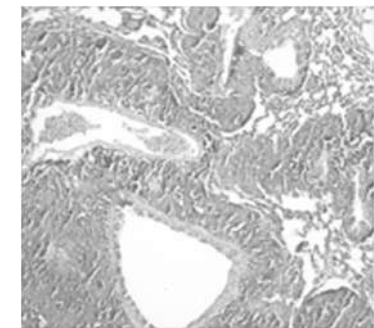
Small cell carcinoma



**Adenocarcinomatous
and small cell areas**



**Adenosquamous
carcinoma**

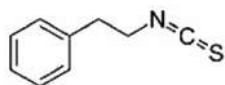


**Low differentiated
carcinoma**

DIETARY AND PHARMACOLOGICAL AGENTS TESTED FOR THE ABILITY TO INTERFERE IN CIGARETTE SMOKE CARCINOGENESIS

De Flora S, Ganchev G, Ilcheva M, La Maestra S, Micale RT, Steele VE, Balansky R., Trends Pharmacol. Sci. 37, 120-142, 2016

Natural agents and miscellaneous drugs



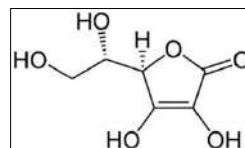
Phenethyl Isothiocyanate



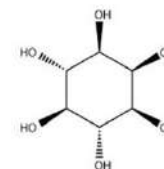
Blackberry



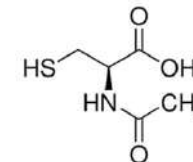
Strawberry



Ascorbic acid

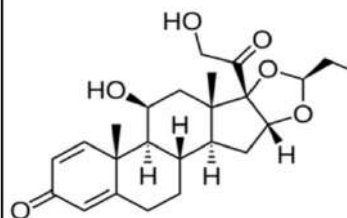


Myo-inositol

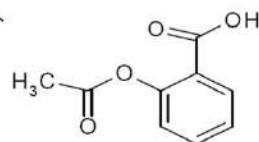


N-Acetylcysteine

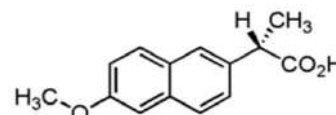
Anti-inflammatory drugs



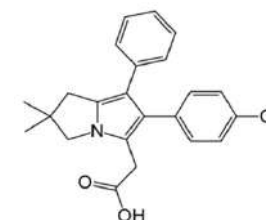
Budesonide



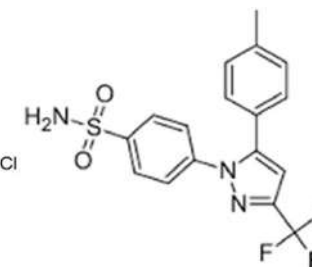
Aspirin



Naproxen

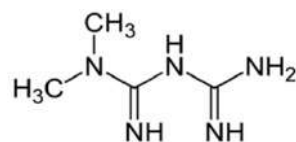


Licofelone

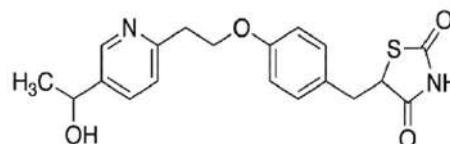


Celecoxib

Antidiabetic drugs

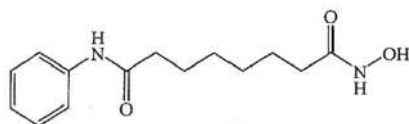


Metformin

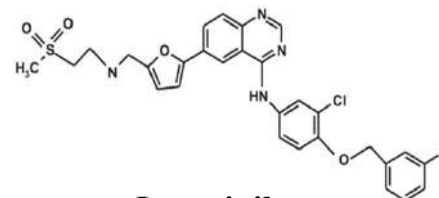


Pioglitazone

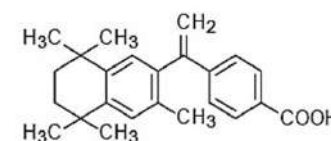
Anticancer drugs



Vorinostat



Lapatinib



Bexarotene

De Flora S, Izzotti A, D'Agostini F, Balansky R.

Mechanisms of N-acetylcysteine in the prevention of DNA damage and cancer,
with special reference to smoking-related end-points.

Carcinogenesis 2001;22: 999-1013.

Nucleophilicity

Antioxidant activity

Antiinflammatory activity

Modulation of metabolism

Effects in mitochondria

Decrease of the biologically effective dose of carcinogens

Modulation of DNA repair

Inhibition of genotoxicity and cell transformation

Modulation of gene expression and signal transduction pathways

Regulation of cell survival and apoptosis

Anti-angiogenetic activity

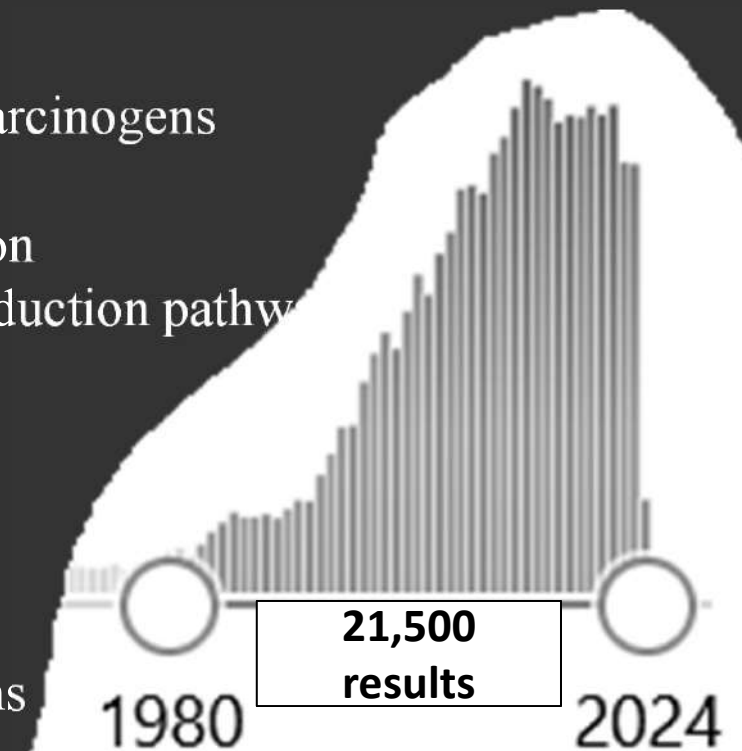
Immunological effects

Inhibition of progression to malignancy

Influence on cell cycle progression

Inhibition of preneoplastic and neoplastic lesions

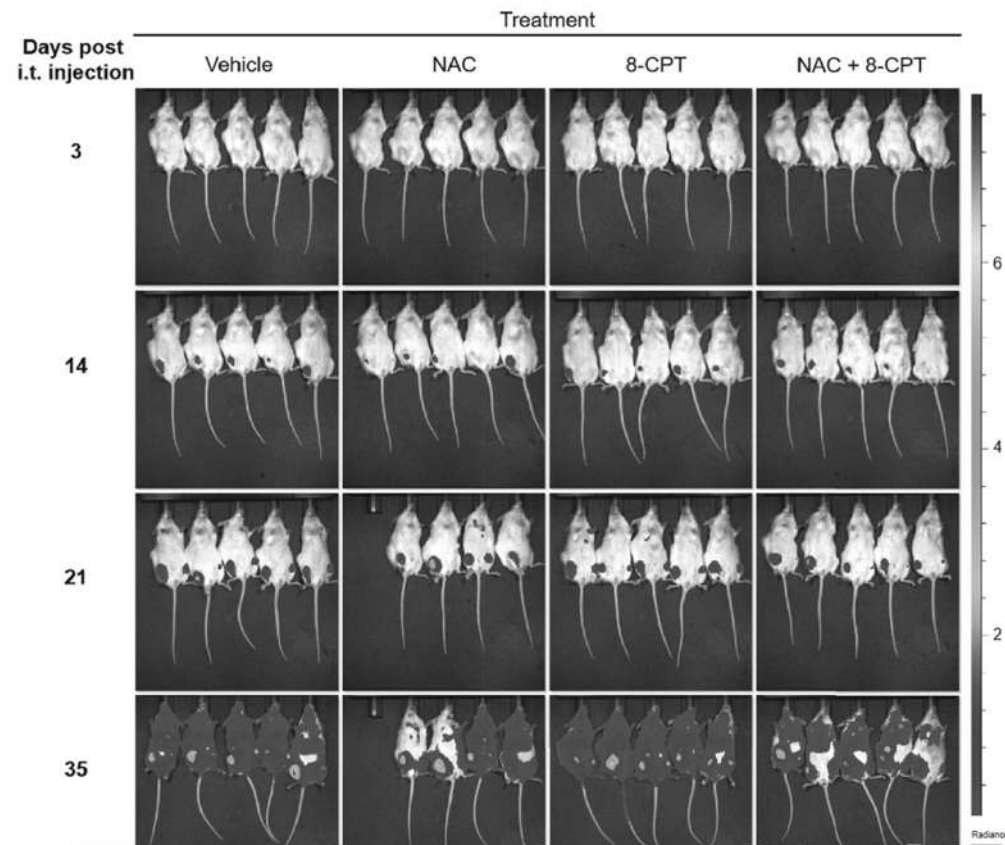
Inhibition of invasion and metastasis



N-acetyl cysteine turns EPAC activators into potent killers of acute lymphoblastic leukemia cells

Nina Richartz¹, Wojciech Pietka¹, Ajay Yadav¹, Monica Bostad², Sampada Bhagwat¹, Soheil Naderi³, Elin Hallan Naderi⁴, Trond Stokke², Ellen Ruud⁵, Heidi Kiil Blomhoff⁶

Taken together, we propose that 8-CPT in the presence of NAC might be utilized as a novel strategy for treating pediatric ALL patients, and that this powerful combination might be exploited to enhance the therapeutic index of current ALL targeting therapies.



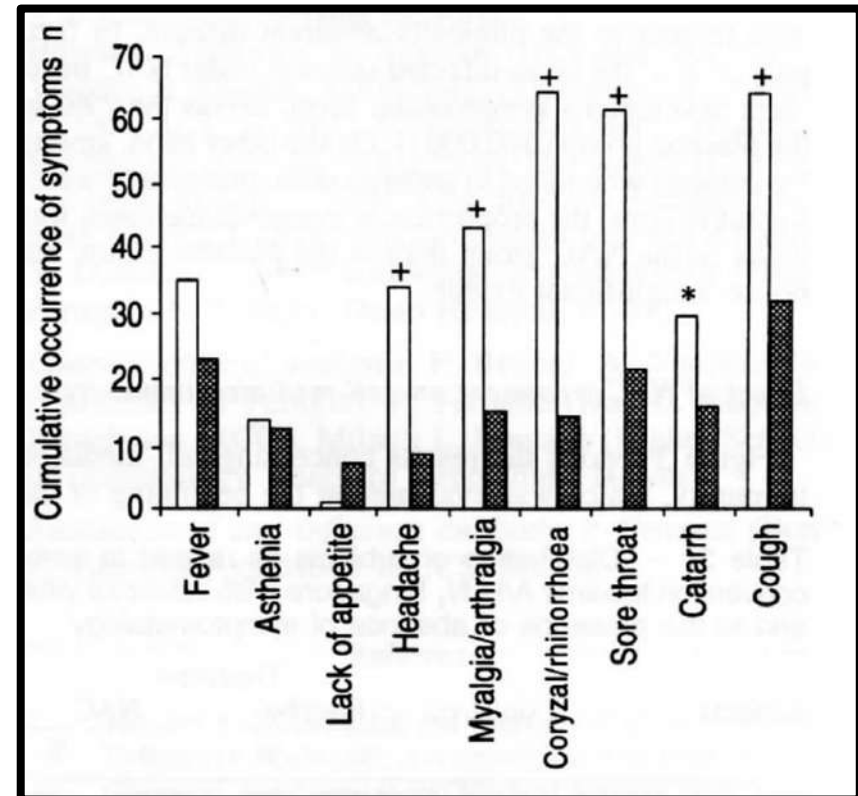
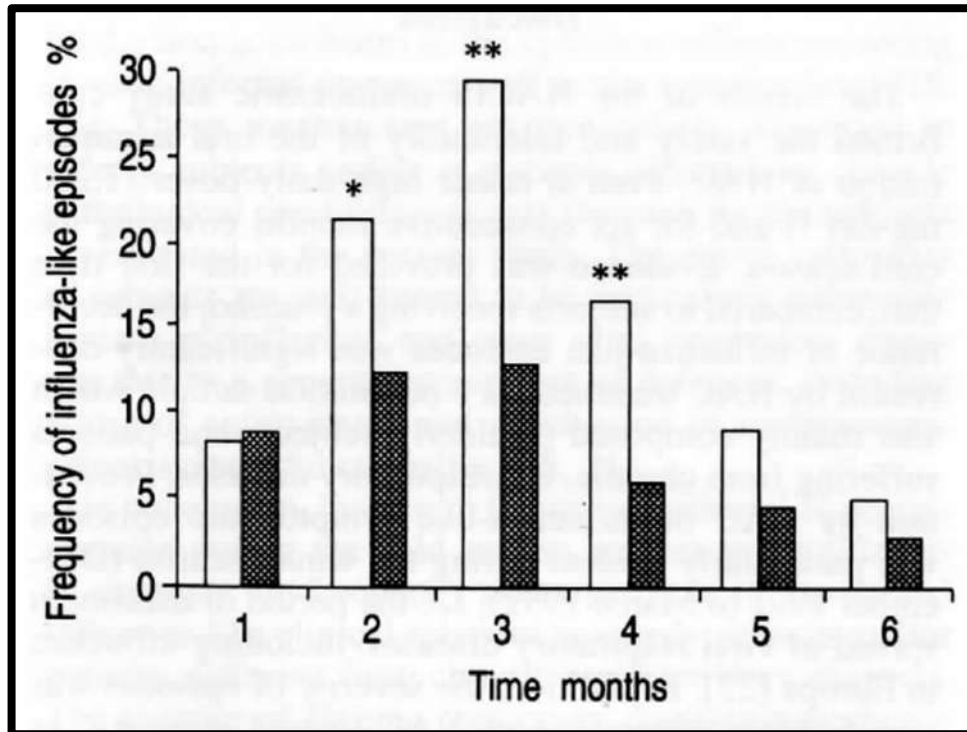
Cysteine induces mitochondrial reductive stress in glioblastoma through hydrogen peroxide production

Evan K Noch^{1, 2}, Laura Palma², Isaiah Yim², Nayah Bullen², Daniel Barnett³, Alexander Walsh³, Bhavneet Bhinder^{4, 5}, Elisa Benedetti^{4, 5}, Jan Krumsiek^{4, 5}, Justin Gurvitch², Sumaiyah Khwaja², Daphne Atlas⁶, Olivier Elemento^{4, 5}, Lewis C Cantley⁷

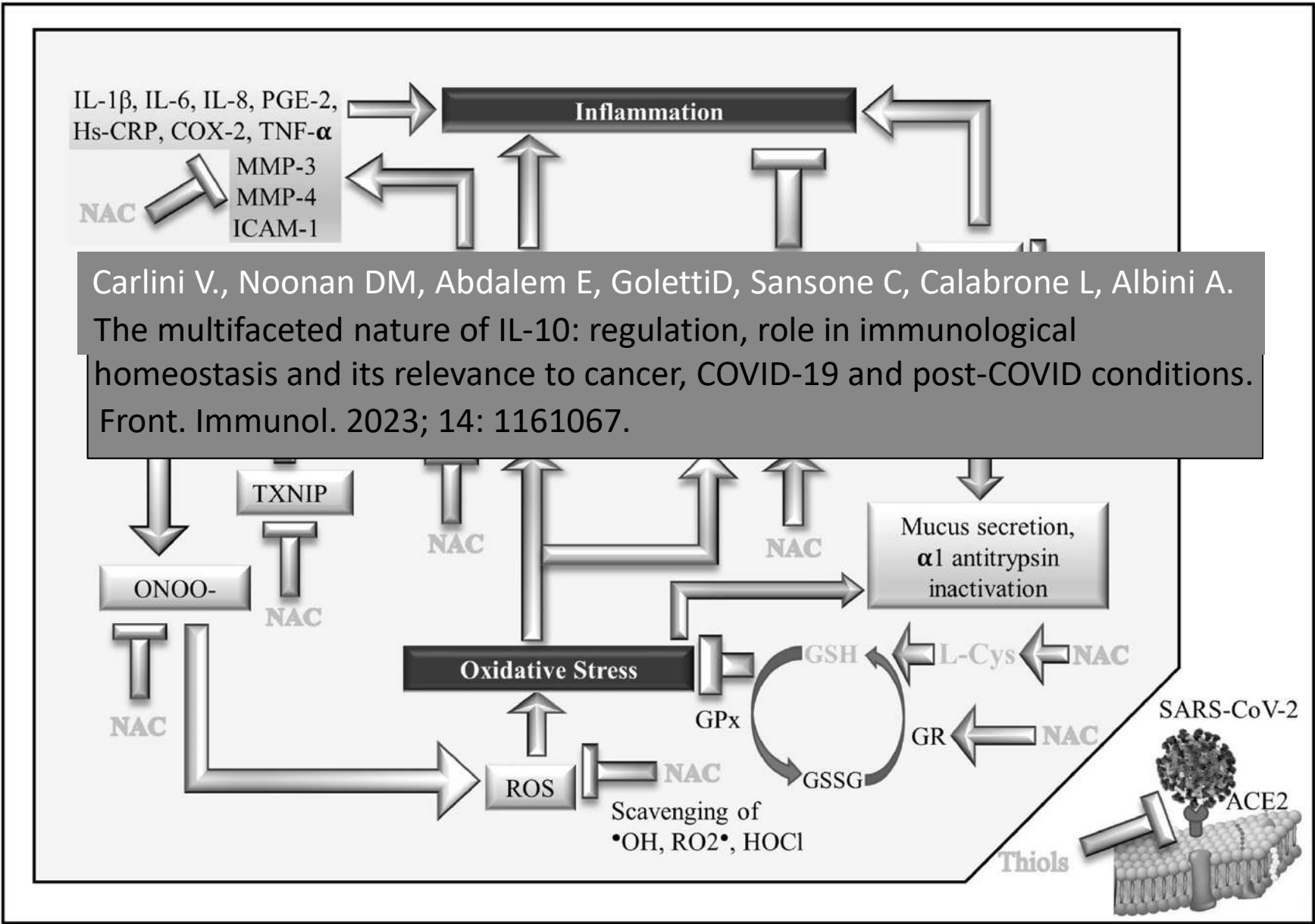
Proceedings of the National Academy of Sciences USA,
2024 Feb.20, e2317343121

Glioblastoma exhibits the highest levels of cysteine and methionine pathway gene expression of 32 human cancers. Treatment of patient-derived glioblastoma cells with the FDA-approved single cysteine compound *N*-acetylcysteine (NAC) reduced cell growth and mitochondrial oxygen consumption. Glioblastoma is uniquely susceptible to NAC-driven reductive stress.

De Flora S., Grassi C., Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term *N*-acetylcysteine treatment. *Eur. Respir. J.*, 10, 1535-1541, 1997.

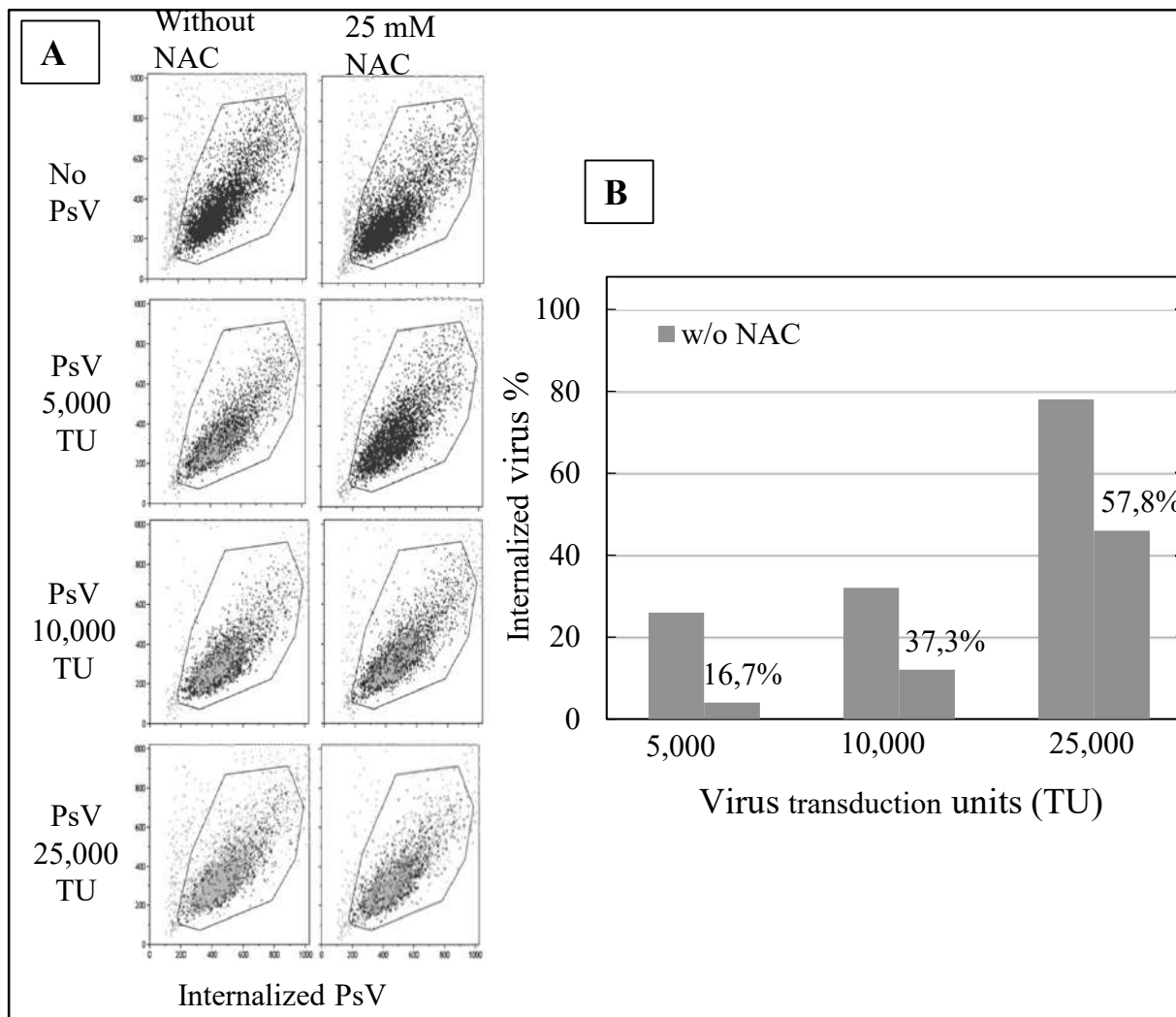


Only 25% of A/H1N1 influenza virus-infected subjects receiving NAC developed a symptomatic form *versus* 79% in the placebo group. A time-related shift of anergic condition to normoergic condition was observed in the NAC group thereby showing a beneficial effect of NAC administration on cell-mediated immunity [7].



Carlini V., Noonan DM, Abdalem E, Goletti D, Sansone C, Calabrone L, Albini A. The multifaceted nature of IL-10: regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. *Front. Immunol.* 2023; 14: 1161067.

S. De Flora, R., Balansky, S. La Maestra. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. *FASEB J* 2020;34:13185-13193.



S. La Maestra, S. Garibaldi, R. Balansky, F. D'Agostini, R.T. Micale, S. De Flora.
 Inhibition of the cell uptake of delta and omicron SARS-CoV-2 pseudoviruses by N-acetylcysteine irrespective of the oxidoreductive environment.

Cells 11, 3313, 2023

MECHANISMS OF CANCER CHEMOPREVENTIVE AGENTS

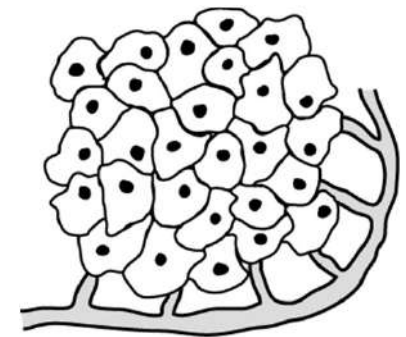
S. De Flora and C. Ramel, *Mutat. Res.*, 202, 285–306, 1988

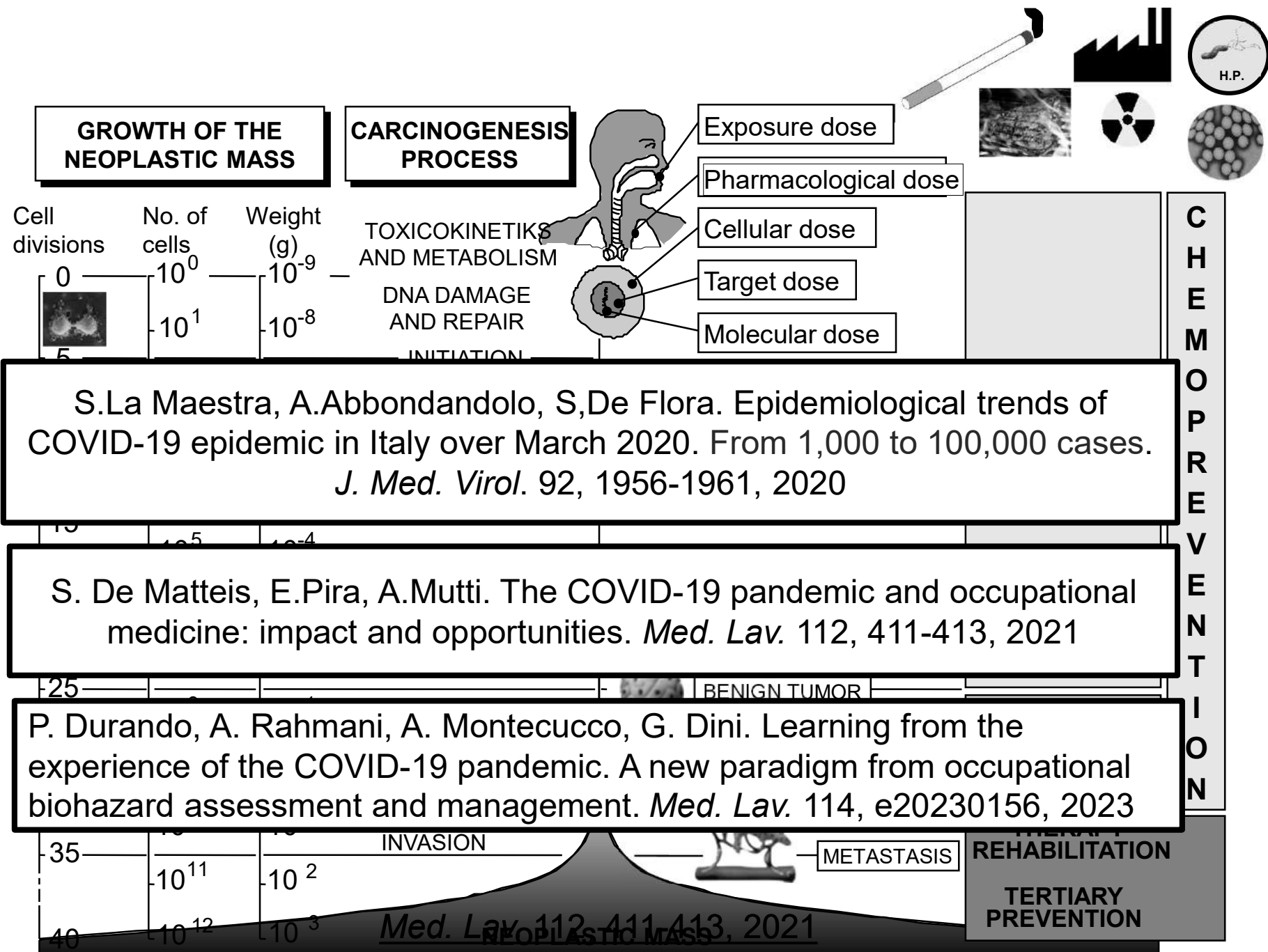
S. De Flora and L.R. Ferguson, *Mutat. Res.*, 591, 8–15, 2005

SECONDARY PREVENTION

4. *Inhibition of tumor progression*

- 4.1. Inhibition of genotoxic effects (see 1 and 2)
- 4.2. Antioxidant activity and scavenging of free radicals
- 4.3. Inhibition of proteases
- 4.4. Signal transduction modulation
- 4.5. Effects on the hormonal status
 - 4.5.1. Selective estrogen receptor modulation
 - 4.5.2. Aromatase inhibition
 - 4.5.3. Selective blocking of prostaglandin E₂ receptors
 - 4.5.4. Decrease in ovarian hormones by dietary isoflavones
 - 4.5.5. Inhibiting the pituitary secretion of luteinizing hormone
 - 4.5.6. Preventing conversion of testosterone into dehydrotestosterone by 5 α -reductase
 - 4.5.7. Selective androgen receptor antagonism
- 4.6. Effects on the immune system
- 4.7. Inhibition of angiogenesis
- 4.8. Antineoplastic activity by either mechanical, physical, chemical, or biological means





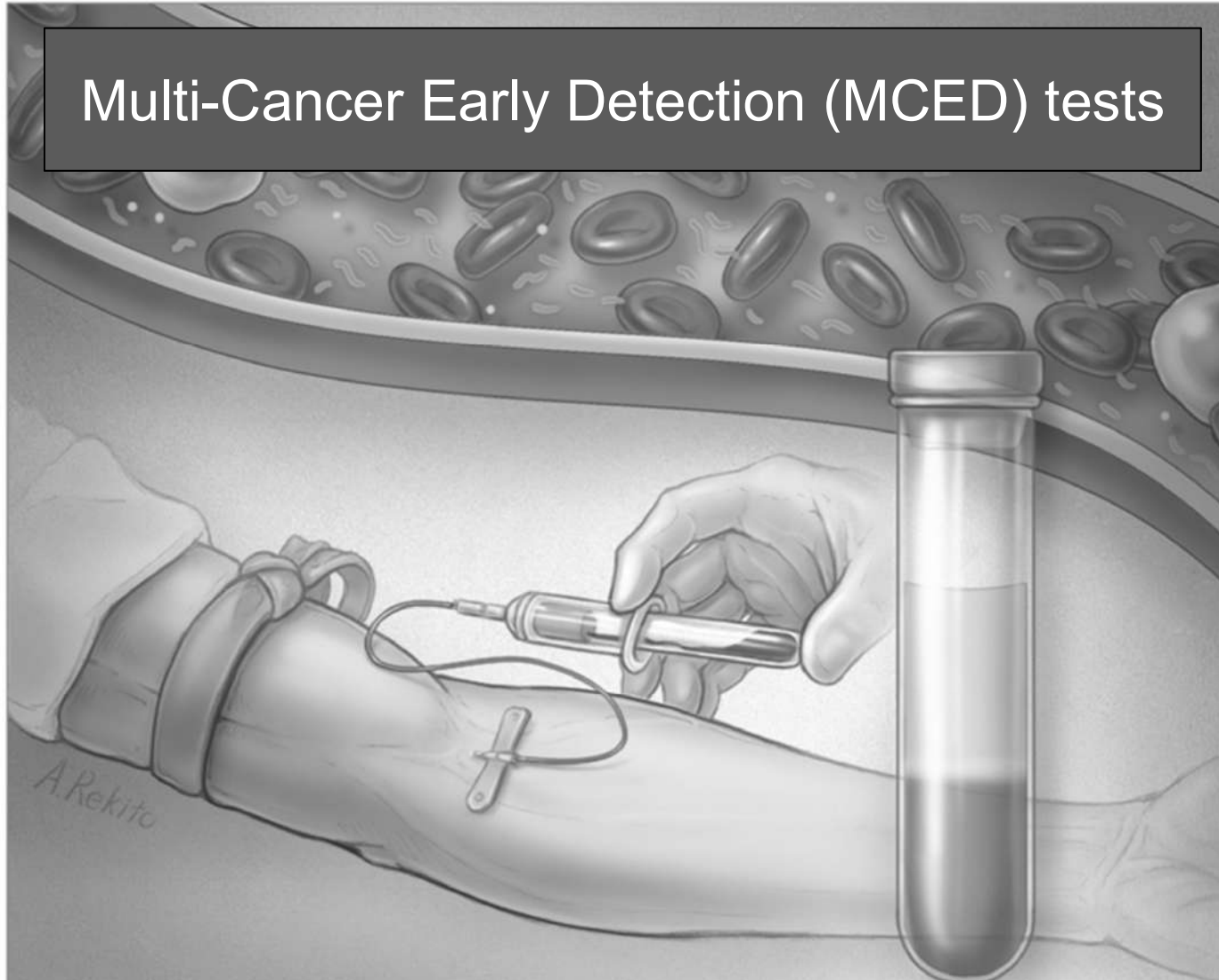
S.La Maestra, A.Abbondandolo, S,De Flora. Epidemiological trends of COVID-19 epidemic in Italy over March 2020. From 1,000 to 100,000 cases. *J. Med. Virol.* 92, 1956-1961, 2020

S. De Matteis, E.Pira, A.Mutti. The COVID-19 pandemic and occupational medicine: impact and opportunities. *Med. Lav.* 112, 411-413, 2021

P. Durando, A. Rahmani, A. Montecucco, G. Dini. Learning from the experience of the COVID-19 pandemic. A new paradigm from occupational biohazard assessment and management. *Med. Lav.* 114, e20230156, 2023

Med. Lav. 112, 411-413, 2021

Multi-Cancer Early Detection (MCED) tests



Farooq M, Leevan E, Shin S, Ahmed J, Ko B, De Souza A, Takebe N.
Blood-based multi-cancer detection: A state-of-the-art update.
Curr Probl Cancer. 2024 Feb; 2023.101059

MECHANISMS OF CANCER CHEMOPREVENTIVE AGENTS

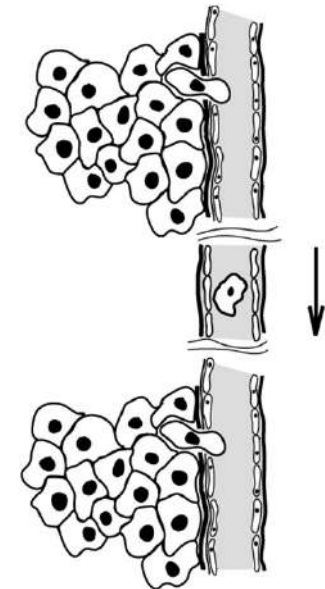
S. De Flora and C. Ramel, *Mutat. Res.*, 202, 285–306, 1988

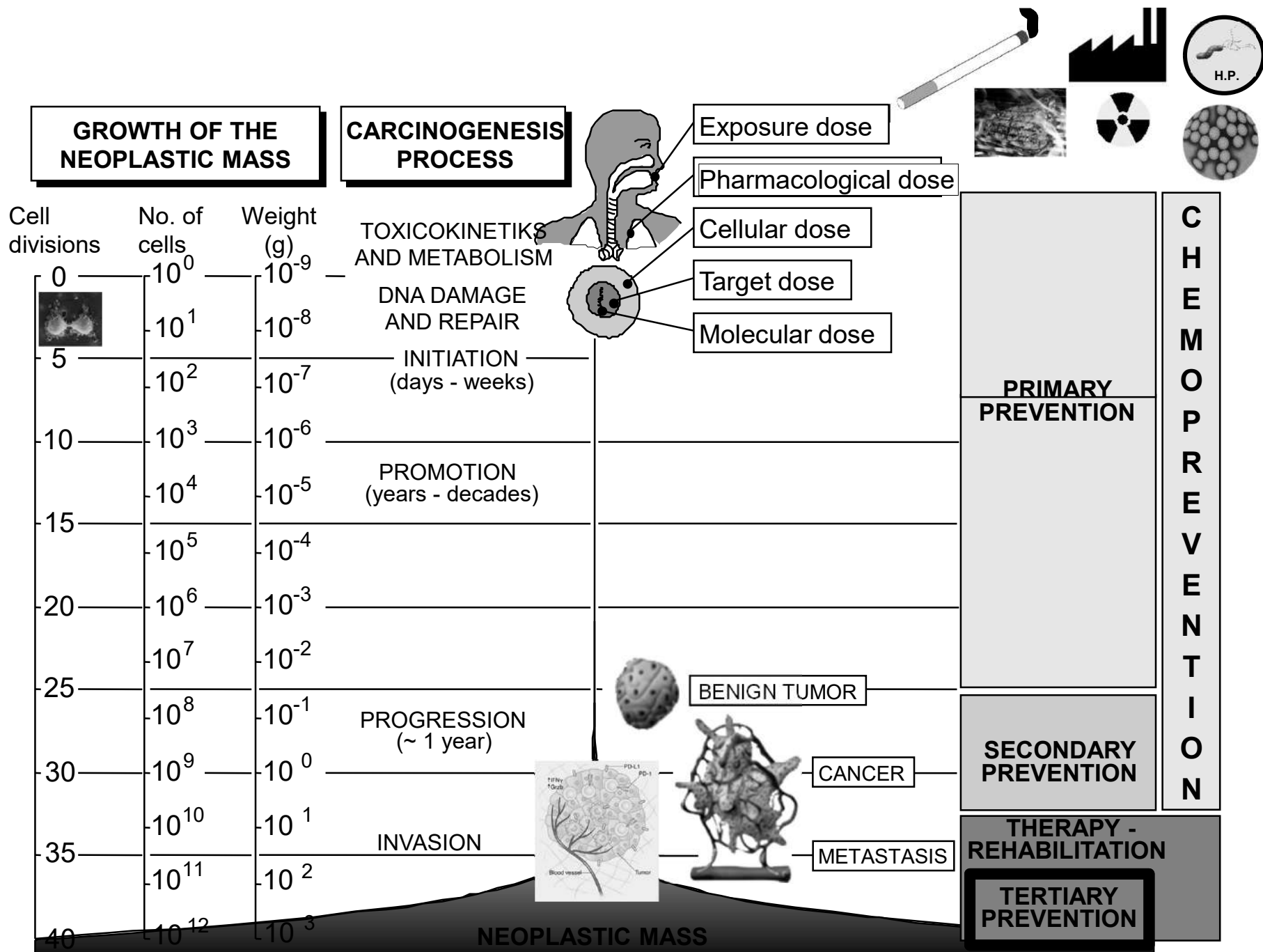
S. De Flora and L.R. Ferguson, *Mutat. Res.*, 591, 8–15, 2005

TERTIARY PREVENTION

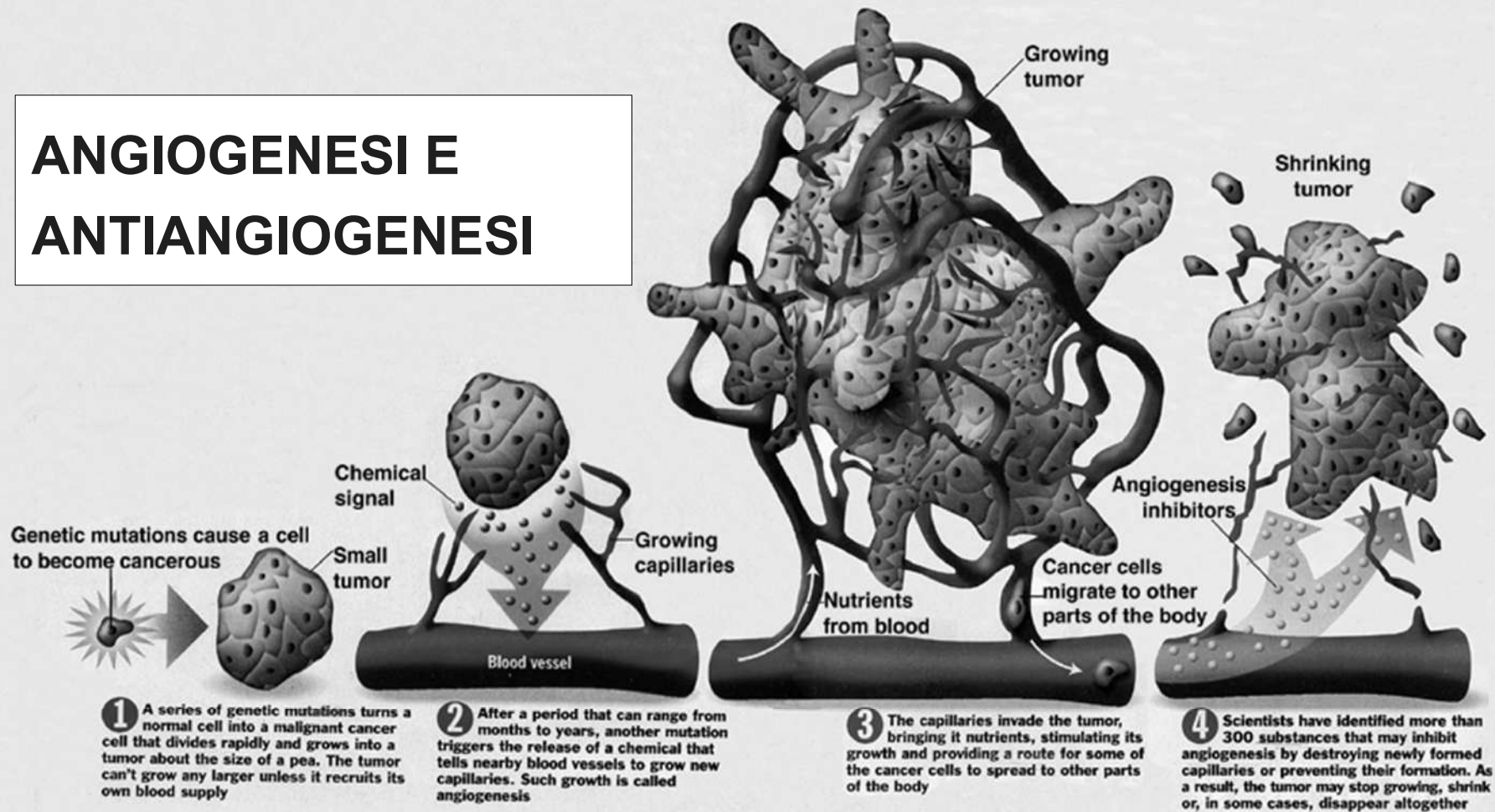
5. *Inhibition of invasion and metastasis*

- 5.1. Antioxidant activity and scavenging of free radicals
- 5.2. Signal transduction modulation
- 5.3. Inhibition of cell proliferation (see 3.4)
- 5.4. Modulation of cell apoptosis
- 5.5. Induction of cell differentiation
- 5.6. Inhibition of angiogenesis
- 5.7. Effect on cell-adhesion molecules
- 5.8. Inhibition of proteases involved in basement membrane degradation and modulation of the interaction with the extracellular matrix
- 5.9. Activation of antimetastasis genes





ANGIOGENESI E ANTIANGIOGENESI



Inhibitors of Angiogenesis

Angiogenesis Inhibitors

Proteins

- Angiostatin
- Endostatin
- Interferons
- Platelet factor 4
- Prolactin 16Kd fragment
- Thrombospondin
- TIMP-1 (tissue inhibitor of metalloproteinase-1)
- TIMP-2 (tissue inhibitor of metalloproteinase-2)
- TIMP-3 (tissue inhibitor of metalloproteinase-3)

Approved by American Society of Hematology

FARMACI ANTIANGIOGENETICI IN COMMERCIO IN ITALIA

Farmaco	Atc	Via di somministrazione	Descrizione	Target	Indicazioni approvate
Bevacizumab	L01XC07	parenterale	anticorpo monoclonale umanizzato	Vegf -A	<ul style="list-style-type: none"> ◆ carcinoma metastatico del colon e del retto ◆ in prima linea: <ul style="list-style-type: none"> - carcinoma mammario metastatico; - carcinoma polmonare non a piccole cellule (Nscic), non resecabile, avanzato, metastatico o in ricaduta, con istologia a predominanza non squamo cellulare; - carcinoma renale avanzato e/o metastatico (Mrcc)
Pegaptanib	S01LA03	intravitreale	aptamero	Vegf -A	degenerazione maculare neovascolare (essudativa) correlata all'età (Amd)
Ranibizumab	S01LA04	intravitreale	anticorpo monoclonale umanizzato	Vegf -A	Amd
Sorafenib	L01XE05	orale	inibitore delle tirosin chinasi a piccola molecola	Vegfr Raf-1	<ul style="list-style-type: none"> ◆ epatocarcinoma ◆ in seconda linea: carcinoma a cellule renali avanzato
Sunitinib	L01XE04	orale	inibitore delle tirosin chinasi a piccola molecola	Vegfr Pdgfr-beta c-Kit	<ul style="list-style-type: none"> ◆ Mrcc ◆ in seconda linea: tumore stromale del tratto gastrointestinale (Gist)

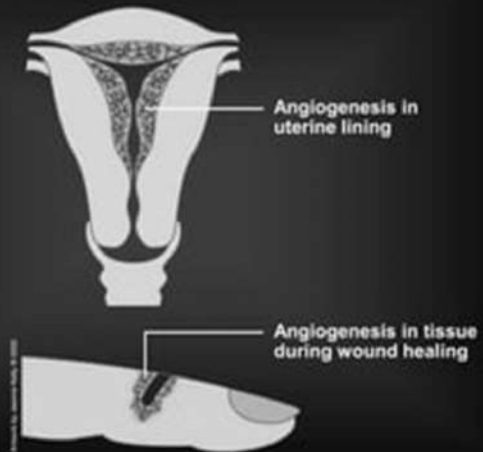
L01XC = Altri antineoplastici, anticorpi monoclonali
 S01LA = Sostanze contro le malattie vascolari oculari, sostanze antineovascolarizzazione
 L01XE = Altri antineoplastici, inibitori della proteina chinasi

Vegf = Fattore di crescita vasculo-endoteliale
 Vegfr = Recettore del Vegf
 Pdgfr = Recettore del fattore di crescita derivato dalle piastrine
 Kit (o Scfr) = Recettore del fattore di crescita per le cellule staminali

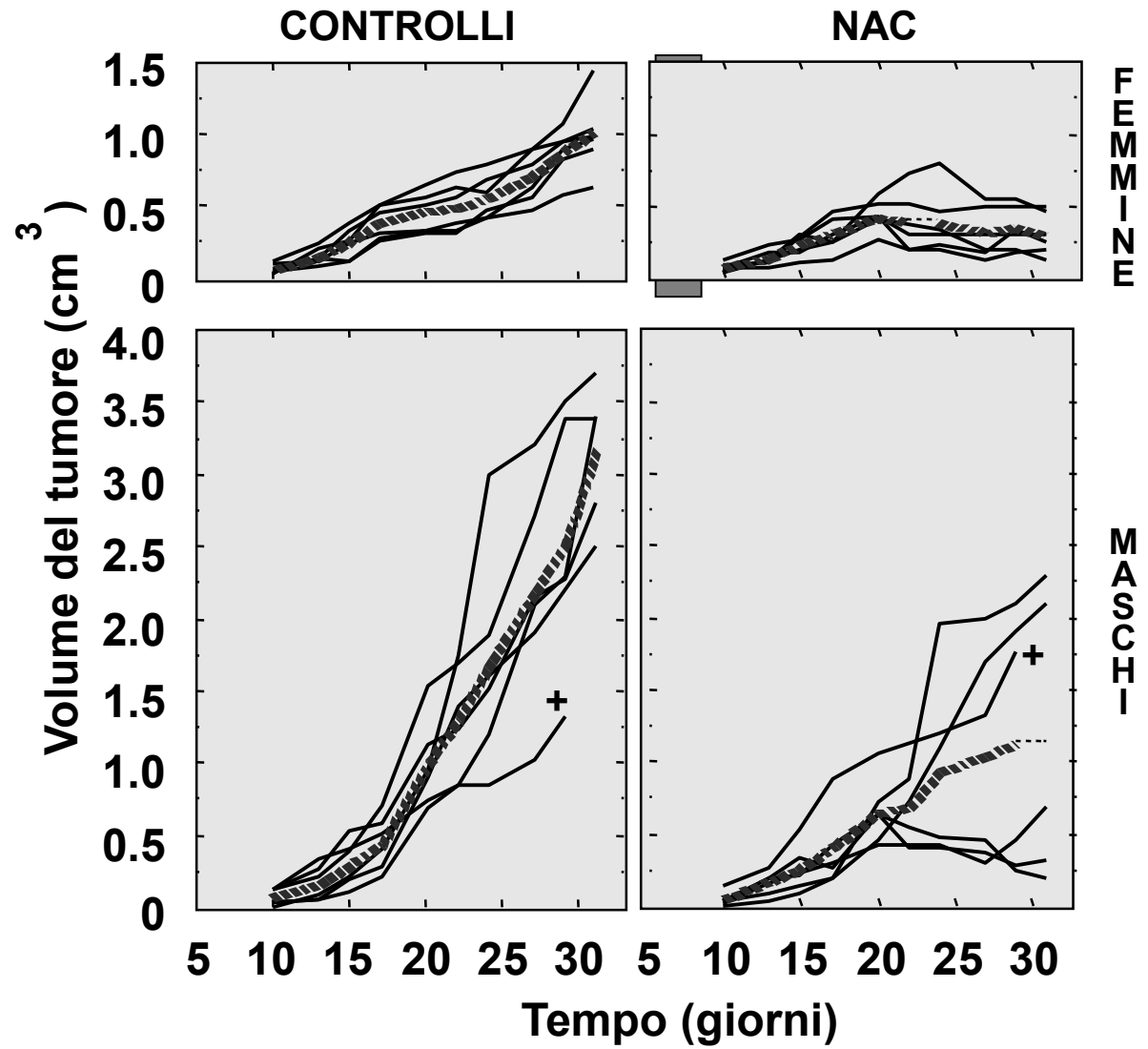
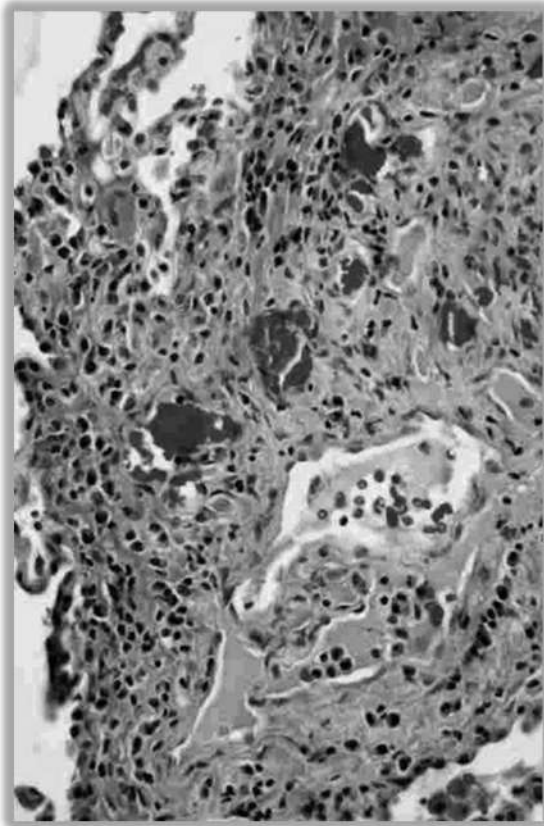
Normal Angiogenesis in Children



Normal Angiogenesis in Adults



CRESCITA DI SARCOMA DI KAPOSÌ UMANO IN TOPI NUDI



A. Albini et al., Cancer Res. 61, 8171-8178, 2001

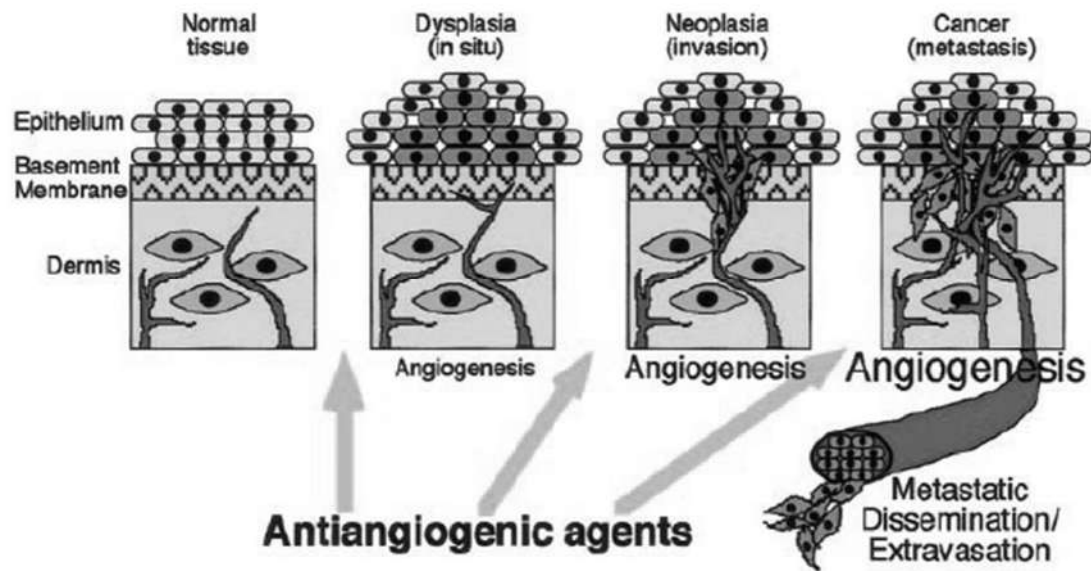
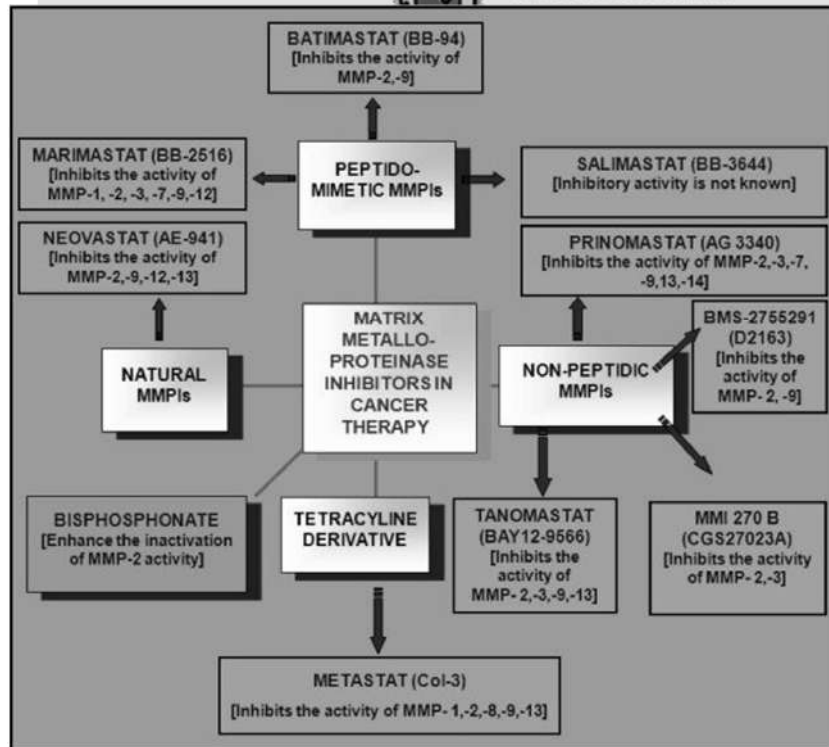
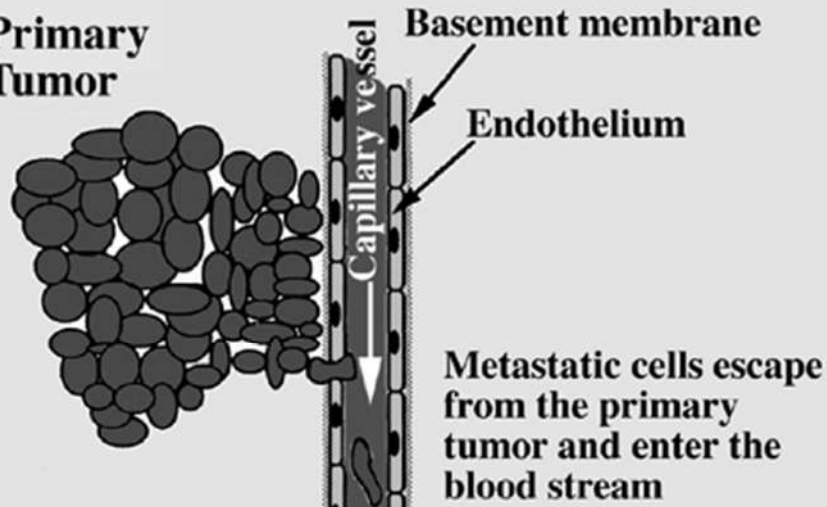


Figure 1. Chemopreventive agents can interfere with the angiogenic process at different stages of tumorigenesis. The 'angiogenic switch' that occurs early during the preneoplastic stages could be curtailed by 'angiopreventive' agents before phenotypic and molecular changes result in the progression from dysplasia to invasive cancer.

'Angioprevention': angiogenesis is a common and keytarget for cancer chemopreventive agents
FRANCESCA TOSETTI, NICOLETTA FERRARI, SILVIO DE FLORA, ADRIANA ALBINI.
F ASEB J. 16, 2-14 (2002)

Extravasation

Primary Tumor



Metastasis

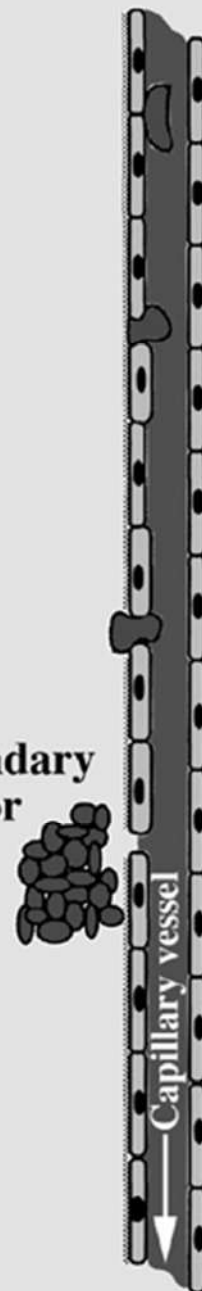
A metastatic cell arrests in the capillary bed of a distant organ

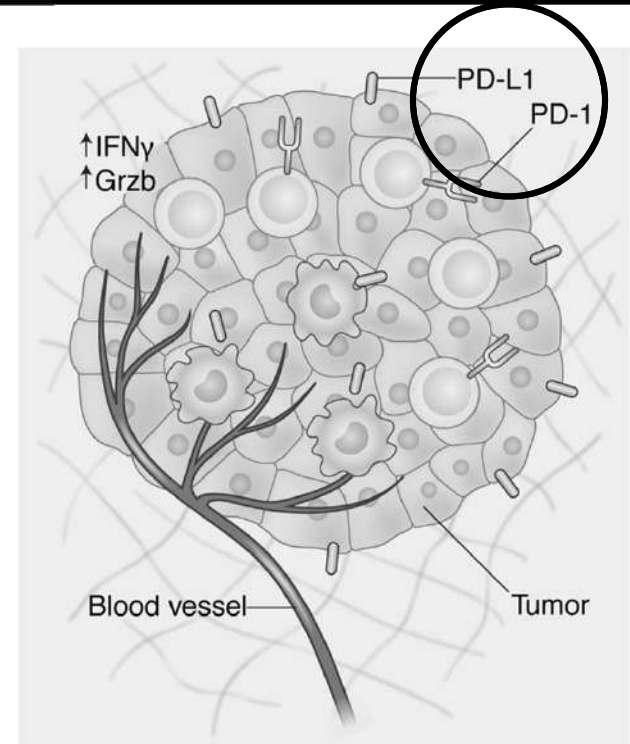
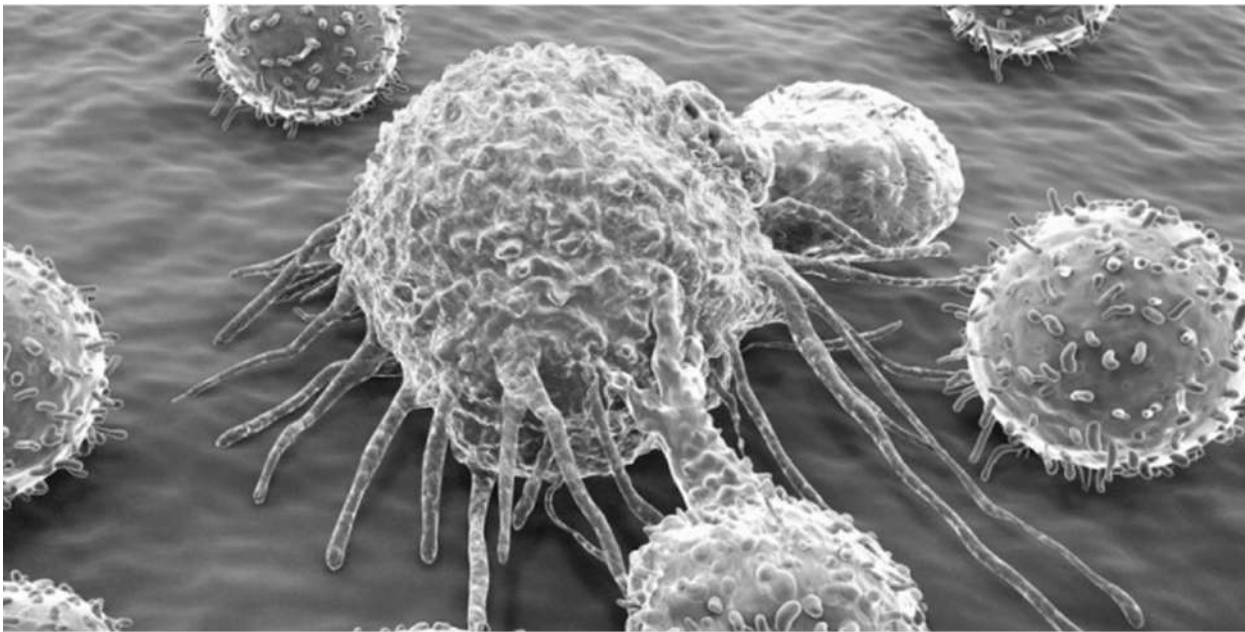
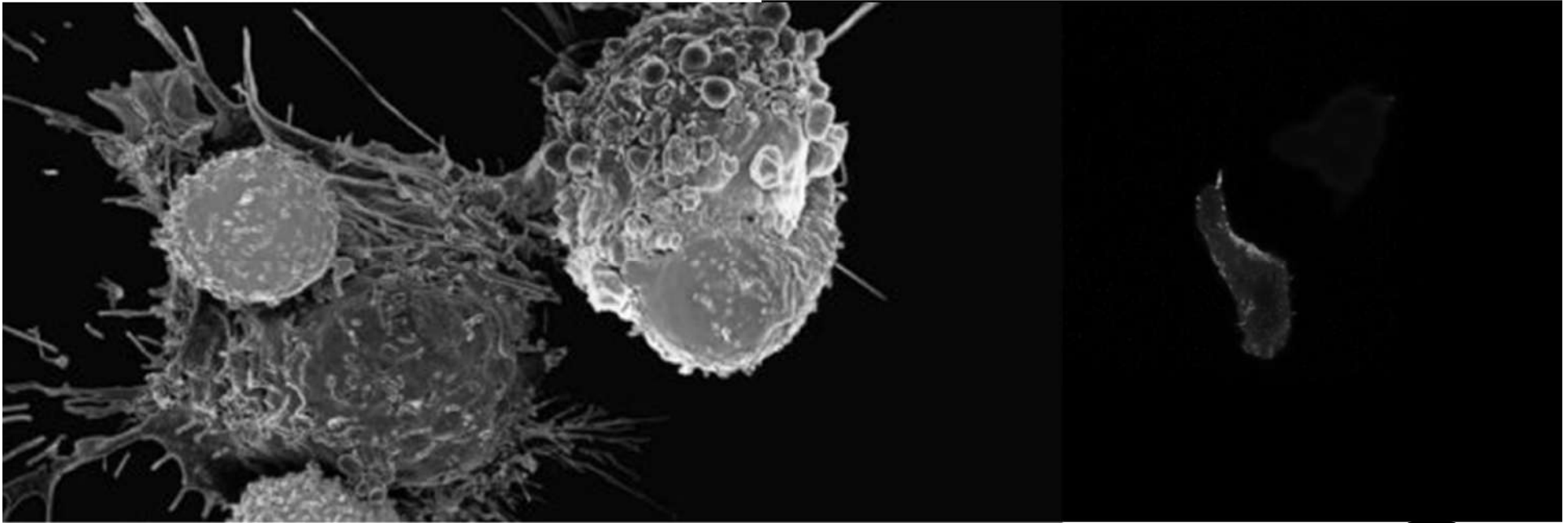
The cell causes retraction of the endothelium and attaches to the basement membrane

The cell secretes proteases which digest the basement membrane. Chemotactic and chemokinetic factors induce the cell to enter the target organ

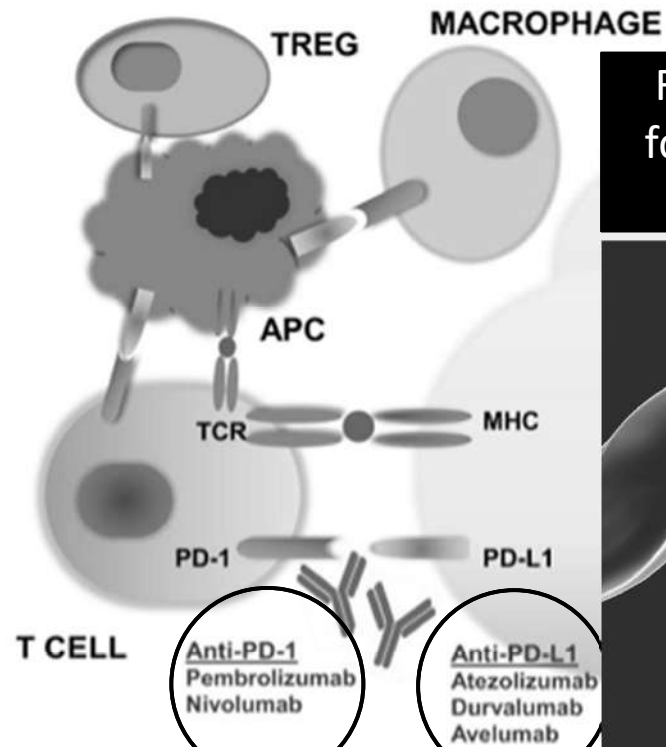
Autocrine and paracrine growth factors stimulate cell proliferation and a secondary tumor is formed. Angiogenesis occurs

Secondary Tumor





Immune checkpoint inhibitors



FDA approves nivolumab plus ipilimumab for the first-line treatment of unresectable malignant pleural mesothelioma



Fig. 1 Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed death-1 (PD-1) receptor on T cells binds to B7-1 (CD80) or B7-2 (CD86) on macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to B7-1 or B7-2 results in suppression of proliferation and immune response of T cells. Activation of PD-1/PD-L1 signaling serves as a principal mechanism by which tumors evade antigen-specific T-cell immunologic responses. Antibody blockade of PD-1 or PD-L1 reverses this process and enhances antitumor immune activity. TCR, T-cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell

Decline in cigarette sales and lung cancer mortality over time

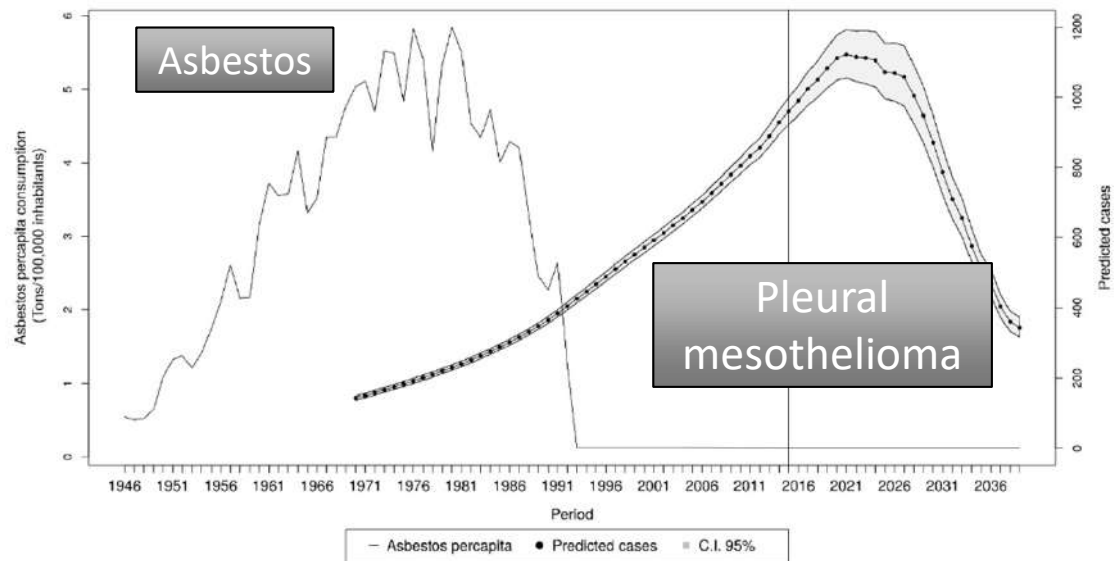
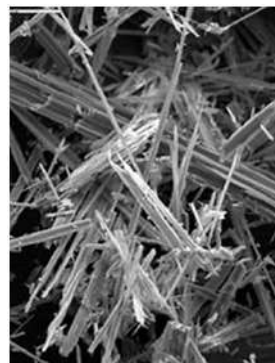
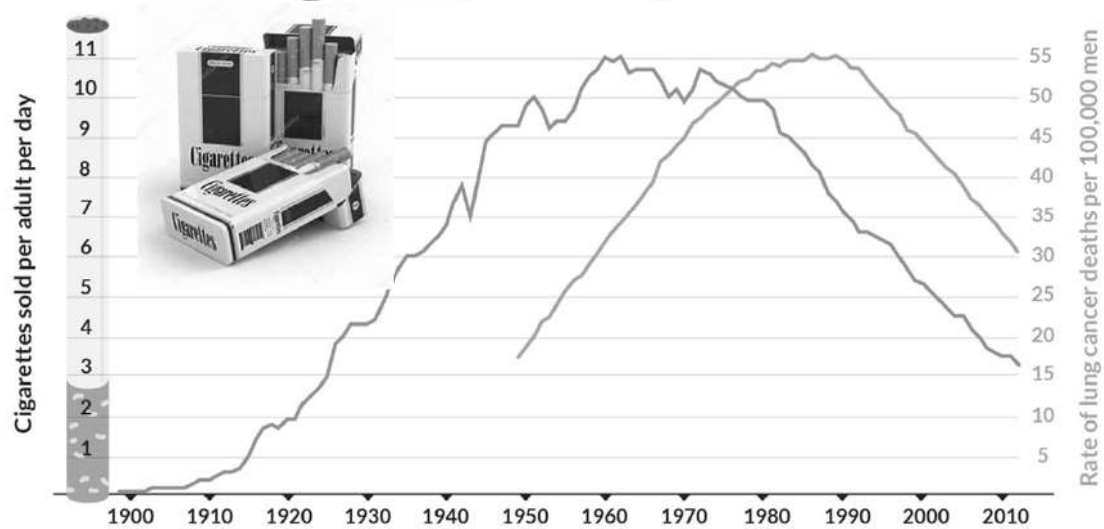


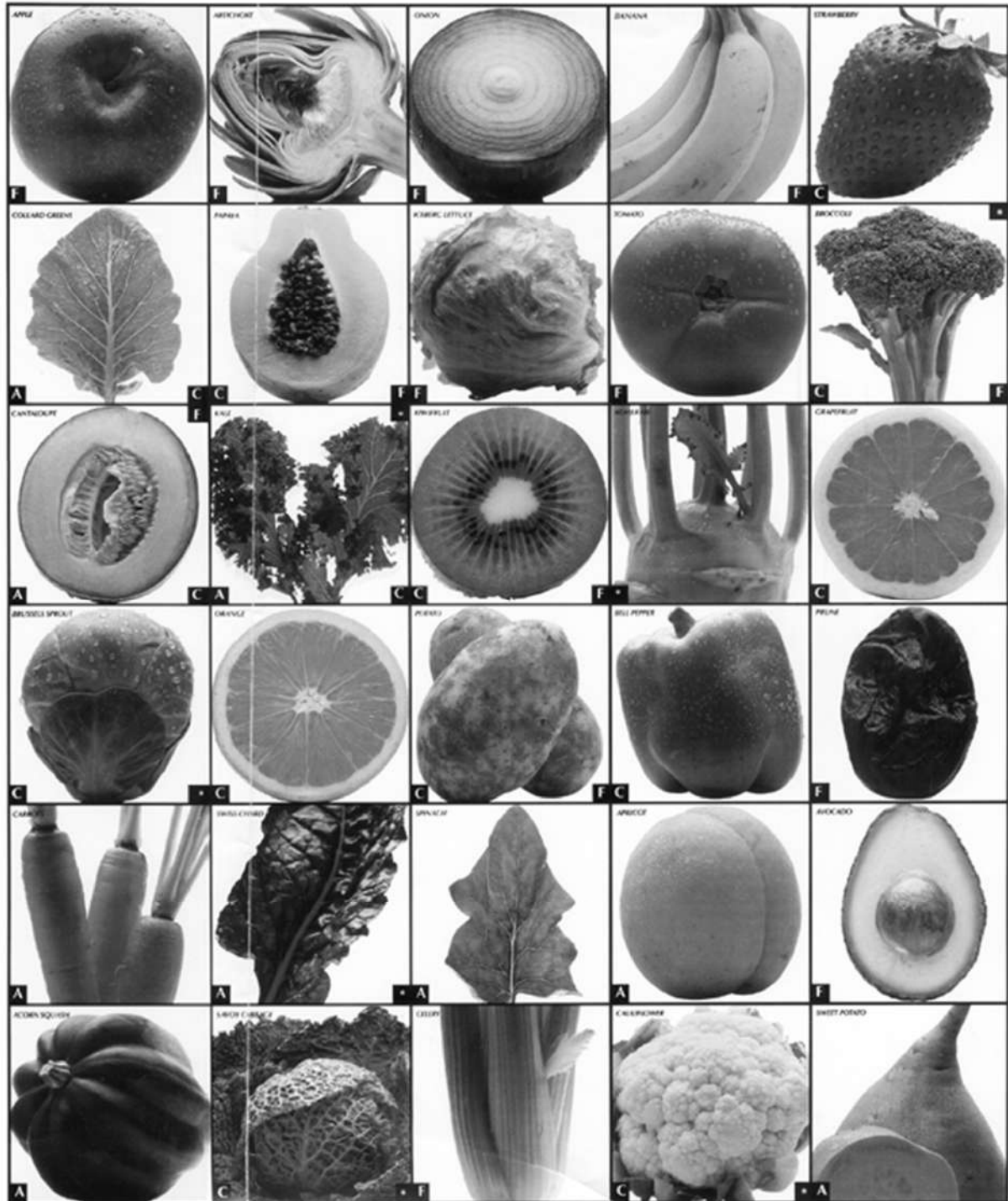
Figure 2. Fitted and predicted (after 2014) MPM cases with related 95% CI. To the left, asbestos per capita consumption in the period 1946–1992 in Italy.

Oddone et al., Cancers 2021

Cancer
**REDUCE
 YOUR
 RISK**

- A** VITAMIN A SOURCE
- C** VITAMIN C SOURCE
- F** FIBER SOURCE
- *** CRUCIFEROUS VEGETABLE

These good food choices may help protect you against certain cancers. For more information on lifestyle choices, contact:



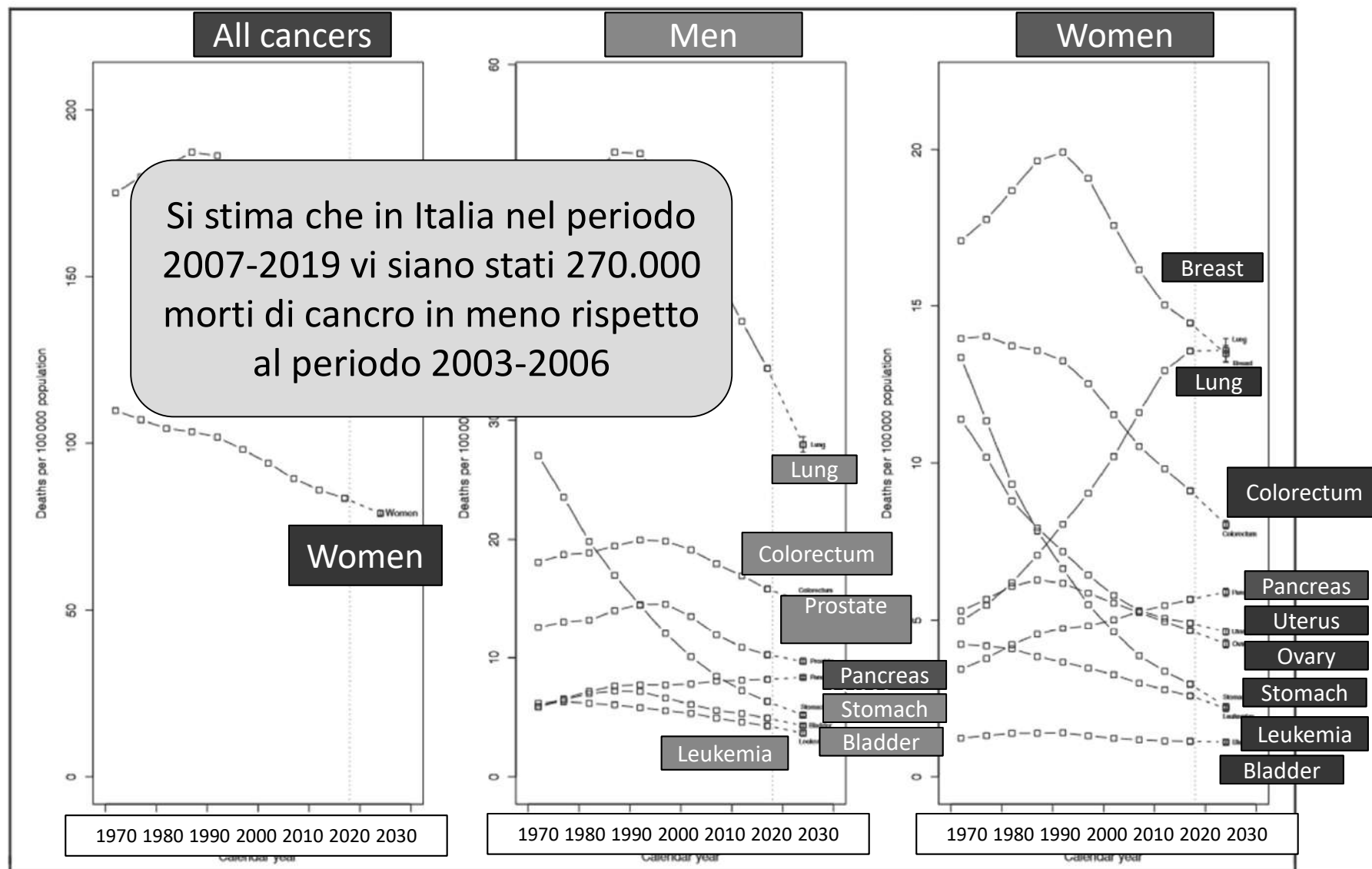


Figure 2. Quinquennial age-standardized (world population) cancer mortality rate trends from 1970-1974 to 2015-2019 and predicted rates for 2024 with 95% prediction intervals, for all cancers combined and both sexes (left) and for major cancer sites in men (center) and women (right), in the EU.

