

Animal carcinogenesis bioassays and the IARC Monographs programme: Recent developments

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GLP Cancer bioassays and the Preamble

- “Agents for which there is sufficient evidence of carcinogenicity in experimental animals also present a carcinogenic hazard to humans” (Preamble to the IARC Monographs)
- 1991 Preamble, criteria for sufficient evidence
 - Positive results “in two or more species of animals or in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.”
 - positive results in one study only led to a default evaluation of limited evidence
- 2006 Preamble, criteria for sufficient evidence
 - Adds: “in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices”

Consequence

- Many agents that would have been classified as Group-3 carcinogens have now been classified as Group 2B/2A
 - studies were mainly from GLP laboratories affiliated to governmental agencies or submitted by the industry to regulatory agencies¹⁻⁵

Volume 101: Chemicals in industrial and consumer products, food contaminants and flavourings, and water chlorination byproducts⁶

	Use, occurrence	Group
2-nitrotoluene*	Dye precursor	2A
1-amino-2,4-dibromoanthraquinone	Dye precursors	2B
Anthraquinone		2B
Cumene	Industrial chemical	2B
Di(2-ethylhexyl)phthalate*	Present in consumer products (plasticiser), food contaminant	2B
Diethanolamine*	Present in consumer products, additive in metalworking fluids	2B
Coconut oil diethanolamine condensate	Present in consumer products	2B
Benzophenone	Industrial chemicals, food flavourings, natural occurrence in food, present in consumer products	2B
2,4-hexadienal		2B
Methyleugenol		2B
Methyl isobutyl ketone		2B
1,3-dichloro-2-propanol	Food processing contaminants	2B
3-monochloro-1,2-propanediol		2B
2-methylimidazole	Industrial chemical	2B
4-methylimidazole	Food contaminant, industrial chemical	2B
Bromochloroacetic acid	Water disinfection byproducts	2B
Dibromoacetic acid		2B
Dibromoacetonitrile*		2B

*Previously evaluated as “not classifiable as to its carcinogenicity to humans” (Group 3).

Table: Agents assessed by the IARC Monograph Working Group

Volume 108: Some drugs and herbal products⁷

	Therapeutic or other use	Group
Pioglitazone	Type 2 diabetes	2A
Rosiglitazone		3
Digoxin	Chronic heart failure and irregular heart rhythm	2B
Hydrochlorothiazide*	Hypertension, by diuresis	2B
Triamterene	Hypertension, by diuresis (combined with other drugs, including hydrochlorothiazide)	2B
Sulfasalazine	Autoimmune arthritis; inflammatory bowel disease	2B
Pentosan polysulfate sodium	Prevention of blood clots; interstitial cystitis	2B
Primidone	Essential tremor	2B
Methylene blue	Nitrate and cyanide poisoning antidote; methaemoglobinemia; psychiatric disorders; disinfectant; microscopic staining agent	3
Whole leaf extract of Aloe vera	Laxative (latex component); food flavouring; in beverages and dietary supplements; cosmetics	2B
Ginkgo biloba extract	Food flavouring; in dietary supplements; medicinal products (peripheral arterial diseases and cerebral insufficiency)	2B
Goldenseal root powder	Prevention and reduction of inflammation and related diseases	2B
Kava extract	In beverages and dietary supplements; cosmetics; medicinal products (anxiety or insomnia)	2B
Pulegone	Component of pennyroyal oils (used to treat dyspepsia and menstrual disorders); and several species of mint (used in foods and beverages)	2B

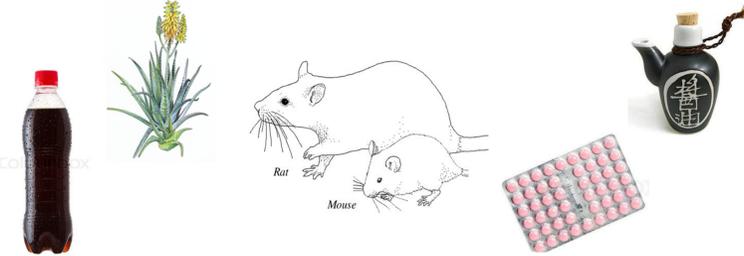
*Previously assessed as “not classifiable as to its carcinogenicity to humans” (group 3).

Table: Agents assessed by the IARC Monograph Working Group

Impact of Bioassay-Driven Evaluations

- Regulatory authorities often have to act on evaluations based predominantly on laboratory data
- Commercial entities sometimes act on evaluations based predominantly on laboratory data
- Much of what is known about mechanisms for chemically-induced carcinogenesis was initiated by, and resulted from, positive animal carcinogenicity data

Agent Studied (monograph)	Use	IARC Classification	Actions Taken
4-Methylimidazole (101)	Contaminant of caramel colorants found in beverages of the cola type	2B	EFSA and WHO/FAO have set levels of ADI Two well-known companies have modified their processes
1,3-Dichloro-2-propanol (101) 3-Monochloro-1,2-propanediol (101)	Formed during food processing, especially for soya sauce and soya-based products	2B	EFSA has set a TDI for 3-MCPD
Whole-leaf extract of Aloe vera (108)	Laxative, food flavouring in beverages, dietary supplement, cosmetics	2B	Industry launched a certification program to guarantee the absence of impurities, specifically toxic anthraquinones Sales suspended in parts of Europe
Pioglitazone (108)	Treatment of Type 2 diabetes	2A	US FDA issued a warning about bladder cancer risk Legal actions underway



The Next Steps

- Revisit previous IARC evaluations where Group-3 agent could be re-evaluated as 2B (ie, 1,2-dichloropropane, Vol. 110)
- Revisit database of studies previously released by governmental agencies worldwide (US NTP, US FDA, Japan Bioassay Research Center, Korean FDA) in preparation of Advisory Group meeting
- Encourage regulatory agencies (eg, European Medicines Agency, US FDA, US EPA) to be more proactive in releasing GLP studies submitted in compliance with the registration process of medicines, pesticides etc.
- Analyse (site-specific) tumour concordance between species
- Prepare scientific articles restricted to subsets of agents or tumour sites

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Tumour (Site) Concordance between Humans and Experimental Animals

- Volumes 100 A-F offer an opportunity to explore many aspects of human to animal concordance
- IARC Monographs programme created a database from the Volumes 100 A-F of agents with sufficient or limited evidence for cancer sites in humans, and sufficient evidence for cancer sites in experimental animals (see excerpt from database below)
- Analyses are underway to evaluate this database (two examples are given below)

Agent	Agent tested in experimental animals	Humans		Animals	
		Sufficient Evidence	Limited Evidence	Sufficient Evidence	Species site
Chlorambucil	Chlorambucil	Acute myeloid leukaemia		lymphoma	Mouse lymphoid tissue
Cyclophosphamide	Cyclophosphamide	Acute myeloid leukaemia, bladder		lymphoma	Mouse lymphoid tissue
Cyclophosphamide	Cyclophosphamide	Acute myeloid leukaemia, bladder		bronchiolo alveolar carcinoma	Mouse lung
Diethylstilbestrol	Diethylstilbestrol	Breast (exposure while pregnant), vagina (clear cell adenocarcinoma, exposure in utero), cervix (clear cell adenocarcinoma, exposure in utero)	Endometrium, cervix (squamous cell carcinoma, exposure in utero), testis (exposure in utero)	renal cell carcinoma	Hamster kidney
Estrogen-only menopausal therapy	Estradiol	Endometrium, ovary		adenocarcinoma	Rat Mammary gland
Arsenic and inorganic arsenic compounds	Dimethylarsinic acid (DMAV), Monomethylarsonous acid (MMAIII), Sodium arsenite	lung, urinary bladder, skin		bronchiolo-alveolar carcinoma	Mouse lung
asbestos (all forms)	Amosite	mesothelioma, lung, larynx, ovary		mesothelioma	Hamster mesothelium
Wood dust		nasal sinus, nasopharynx		adenocarcinoma	Rat Mammary Gland
X- and Gamma radiation	X- and Gamma radiation	Salivary gland, oesophagus, stomach, colon, lung, bone, basal cell of the skin, female breast, urinary bladder, brain and CNS, thyroid, kidney, leukaemia (excl. chronic lymphocytic leukaemia). In-utero exposure causes cancer (above-mentioned cancers and childhood cancers)	Rectum, liver, pancreas, ovary, prostate, non-Hodgkin lymphoma, multiple myeloma		
tobacco smoking	tobacco smoke	lung, liver, kidney, pancreas, ureter, urinary bladder, uterine cervix, ovary, myeloid leukaemia, oral cavity, nasal cavity, paranasal sinuses; naso-, oro-, hypopharynx; larynx, oesophagus, stomach, colorectum, hepatoblastoma in children (parental smoking)	breast, childhood leukemia (acute lymphocytic leukaemia) (parental smoking)	bronchiolo-alveolar carcinoma	Mouse lung
Benzene	Benzene	Acute myeloid leukaemia/acute non-lymphocytic leukaemia		carcinoma	Mouse Zymbal gland
Benzo[a]pyrene	Benzo[a]pyrene			adenocarcinoma	Hamster Lung
2,3,7,8-Tetrachlorodibenzo-para-dioxin	2,3,7,8-TCDD	All cancers combined		Soft-tissue sarcoma, non-Hodgkin lymphoma, lung	Mouse Lymphoid tissue

Preliminary analysis of agreement between agents that cause haematopoietic tumours in humans and experimental animals

Agent	Humans	Mice	Agreement	Tissue Examined	Two studies
Chlorambucil	Hematopoietic tumours	Lymphosarcomas and granulocytic leukemias	Y	Y	Y
Cyclophosphamide	Hematopoietic tumours	Lymphomas and possibly lymphoid tumors	Y	Y	Y
Benzene	Hematopoietic tumours	Thymus lymphoma, lymphoid tissue lymphoma, granulocytic leukemia Non-Hodgkins	Y	Y	Y
Azathioprine	Hematopoietic tumours	lymphoma, Thymus lymphoma, lymphoid tissue lymphoma	Y	Y	Y
X and gamma radiation	Hematopoietic tumours	Thymus lymphoma, lymphoid tissue lymphoma, granulocytic leukemia	Y	Y	Y
Th-232	Hematopoietic tumours	Other sites (no data on hematopoietic tumours)	NA	N	N
Sr-90	Leukemias excluding CLL	Lymphoid tumours	Y	Y	N
I-131	Leukemias	No mouse data	NA	NA	NA
Rn-222	Leukemias	No mouse data	NA	NA	NA
Neutrons	Hematopoietic tumours (insufficient)	Thymus lymphoma, lymphoid tissue lymphoma, granulocytic leukemia	Y	Y	Y
Tobacco smoke	Hematopoietic tumours	Negative (subject to review)	N	Y	Y
Butadiene	Hematolympathic organ tumors	Lymphomas	Y	Y	Y
Thiotepa	Leukemias	Malignant lymphoma and lymphocytic leukemia	Y	Y	Y
Ethylene oxide	Lymphatic and hematopoietic tumors	Malignant lymphomas in females (limited evidence)	Y	Y	N
Formaldehyde	Leukemia	Negative	N	Y	N

Frequency of species developing tumours at similar sites

Agent	Tissue/System						
	Upper Aerodigestive tract and respiratory system	Digestive system	Nervous and endocrine system	Urinary system	Lymphoid and hematopoietic system	Skin and connective tissue	Female reproductive organs
Chlorambucil							
Cyclophosphamide							
Diethylstilbestrol							
Estrogen							
Arsenic							
Asbestos (all forms)							
Wood dust							
X and gamma radiation							
Tobacco							
Benzene							
Benzo-a-pyrene							
2,3,7,8-tetrachloro-para-dioxin							

■ Humans and 3 animal species ■ 4 animal species and inadequate for humans
■ Humans and 1 animal species ■ 2 animal species and inadequate for humans
■ Humans only ■ 1 animal species and inadequate for humans

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