DRAFT PRIORITIZED CANDIDATE CHEMICALS UNDER CONSIDERATION FOR CARCINOGENICITY EVALUATION:

BATCH #4

Office of Environmental Health Hazard Assessment California Environmental Protection Agency

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Draft data summaries for 50 chemicals under consideration for carcinogenicity evaluation ("Batch #4") have been prepared and are presented here. The same process utilized to select the previous group of chemicals prioritized for carcinogenicity concern (*i.e.*, Batch #3) was employed in the selection of the Batch #4 chemicals. Namely, 50 chemicals were randomly selected from 100 chemicals in the tracking database. The 100 chemicals consisted of the 39 chemicals remaining from the previous random selection and 61 additional chemicals selected using a table of random numbers from among those chemicals in the database that are produced, used, released or present in California, and for which there is some information suggesting the chemicals may be carcinogenic. Prioritization of Batch #4 chemicals proceeded as described in the document entitled "Procedure for Prioritizing Candidate Chemicals for Consideration Under Proposition 65 by the State's Qualified Experts" (May 1997). Today marks the start of a 60-day public comment period on the draft data summaries for these 50 selected chemicals. A public workshop will be held on November 19, 2003 to receive verbal comments. Public comments received on the data summaries during the 60-day comment period will be reviewed and considered as part of the assignment of final priorities.

Prioritized chemicals with a final priority of "High" Carcinogenicity Concern are assigned to the Candidate List, from which chemicals will be chosen for the preparation of hazard identification documents. All chemicals not assigned a final "high" level of carcinogenic concern are assigned to Category II. Action is not anticipated on Category II chemicals until all high priority chemicals on the Candidate List with known or potential exposure have been evaluated.

It should be noted that (1) this prioritization process reflects a preliminary, rather than an indepth review of carcinogenicity and exposure data, and, (2) the process is a continuous one; efforts to gather additional information on Category I and Category II chemicals are ongoing.

Name of Chemical	CAS No.	Level of Exposure Concern	Page
On Candidate List due to HIGH CARCINOGENIO	ITY CONCERN	l)	
4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzene sulfonamide (sulfamethazine)	57-68-1	high	4
3,6-Dinitrobenzo[a]pyrene	128714-76-1	high	6
1,2-Epoxybutane	106-88-7	high	7
Methimazole	60-56-0	high	9
Molybdenum trioxide	1313-27-5	high	11
4-Nitrotoluene (<i>p</i> -nitrotoluene)	99-99-0	high	13
Nucleoside analogues: 3'-Azido-3'-deoxythymidine (AZT, zidovudine, N ₃ -ddT); 2',3'-Dideoxycytidine (ddC, zalcitabine); Stavudine (d4T); Trifluridine	30516-87-1 7481-89-2 3056-17-5 70-00-8	<mark>high</mark> high high high	15
Propoxur (Baygon)	114-26-1	high	17
Titanium dioxide	13463-67-7	high	19
1,2,4-Trichlorobenzene	120-82-1	high	21
Verapamil	52-53-9	high	23
2-Chloro-1,1,1-trifluoroethane	75-88-7	medium	25
4-Hydroxybenzenediazonium and its salts	19089-85-1	medium	27
4-Methylbenzenediazonium and its salts	57573-52-1	medium	29
Ciprofibrate	52214-84-3	low	31
Diallate	2303-16-4	n.i.c.	33
Diftalone	21626-89-1	n.i.c.	34
Category II (Not HIGH CARCINOGENICITY CON	CERN)		
Acephate	30560-19-1	high	35
trans-Anethole	4180-23-8	high	37
Aspartame	22839-47-0	high	39
Chloroacetic acid	79-11-8	high	42
Chloromethane (methyl chloride)	74-87-3	high	44
Cholestyramine	11041-12-6	high	46
Clofentezine	74115-24-5	high	48
Cycloate	1134-23-2	high	49
3,4-Dihydrocoumarin	119-84-6	high	50
Flutamide	13311-84-7	high	52
Isoniazid	54-85-3	high	54

CARCINOGENICITY DATA SUMMARY: NUCLEOSIDE ANALOGUES: 3'-AZIDO-3'-DEOXYTHYMIDINE (AZT, ZIDOVUDINE, N₃-DDT), 2',3'-DIDEOXYCYTIDINE (DDC, ZALCITABINE), STAVUDINE (D4T), TRIFLURIDINE

Preliminary evaluation of carcinogenicity and exposure data

There is a **HIGH level of carcinogenicity concern over 3'-azido-3'-deoxythymidine** [AZT, zidovudine, N₃-ddT; CAS No. 30516-87-1], **2', 3'-dideoxycytidine** [ddC, zalcitabine; CAS No. 7481-89-2], **stavudine** [d4T; CAS No. 3056-17-5], and **trifluridine** [CAS No. 70-00-8], sufficient for these chemicals to be placed on the candidate list. The concern over these chemicals stems from observations of squamous cell carcinoma of the vagina among rodents exposed to 3'-azido-3'-deoxythymidine (AZT) as adults (Ayers *et al.*, 1996, 1997; NTP, 1999) and tumors at various sites following transplacental exposure of mice to AZT (Ayers *et al.*, 1997; Olivero *et al.*, 1997; Diwan *et al.*, 1999); lymphomas among male and female mice treated with 2',3'-dideoxycytidine (ddC) (Sanders *et al.*, 1995; Rao *et al.*, 1996); benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats treated with stavudine (d4T) (PDR, 2000); and malignant cancers of the intestines, mammary gland and prostate in rodents treated with trifluridine (PDR, 2000); evidence of genotoxicity; and structural or functional similarities with the carcinogen azacytidine.

Nucleoside analogues are chemically-modified DNA or RNA bases, used primarily as anti-neoplastic and antiviral drugs. The chemical modifications can be on the nucleotide base or the sugar moiety or both. Nucleoside analogues function to inhibit DNA or RNA synthesis or to interfere with nucleic acid synthesis, resulting in alterations in DNA replication, gene function, and other vital cellular processes. Nucleoside analogues act by various mechanisms to inhibit DNA and RNA synthesis, including (1) incorporation into DNA or RNA, effectively terminating further strand synthesis, and (2) inhibition of DNA polymerase or related enzymes involved in DNA or RNA synthesis (Calabresi and Chabner, 1989; Douglas, 1989; Phillips *et al.*, 1991; PDR, 2000; IARC, 2000).

Other nucleoside analogues exhibit evidence of carcinogenicity, based on increases in benign mammary, pancreatic and adrenal tumors in rats treated with rabavirin (PDR, 2000), observations of genotoxicity, primarily in mammalian cell assays, for brivudine, cytarabine, dideoxyadenosine, dideoxyinosine, fludarabine, gemcitabine, pentostatin, rabavirin, vidarabine (Simpson *et al.*, 1989; Calabresi and Chabner, 1989; Mamber *et al.*, 1990; Phillips *et al.*, 1991; PDR, 2000, Nabhan *et al.*, 2001; IARC, 2000; CCRIS, 2002; GENE-TOX, 2002), and structural or functional similarities with the carcinogen azacytidine.

IARC classified AZT and 2', 3'-dideoxycytidine (zalcitabine, ddC) as possibly carcinogenic to humans (Group 2B) based on inadequate data in humans and sufficient evidence in animals (IARC, 2000).

IARC classified 2',3'-dideoxyinosine (ddI) and aciclovir as Group 3 (not classifiable as to its carcinogenicity) based on inadequate data in human and animals (IARC, 2000).

There is a **HIGH** level of **concern over the extent of exposure.** Many of the nucleoside analogues are approved drugs used to treat viral infections, cancer, or other diseases (PDR, 2000).

References

Ayers KM, Clive D, Tucker WE Jr, Hajian G, de Miranda P (1996). Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats. *Fundam Appl Toxicol* **32**(2):148-58.

Ayers KM, Torrey CE, Reynolds DJ (1997). A transplacental carcinogenicity bioassay in CD-1 mice with zidovudine. *Fundam Appl Toxicol* **38**(2):195-8.

Calabresi P, Chabner BA (1989). Chemotherapy of neoplastic diseases. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, pp. 1202-1236.

Chemical Carcinogenesis Research Information System (CCRIS, 2002). National Library of Medicine, National Institutes of Health. Available at: http://toxnet.nlm.nih.gov/. Access date: March 2002.

Diwan BA, Riggs CW, Logsdon D, Haines DC, Olivero OA, Rice JM, Yuspa SH, Poirier MC, Anderson LM (1999). Multiorgan transplacental and neonatal carcinogenicity of 3'-azido-3'-deoxythymidine in mice. *Toxicol Appl Pharmacol* **161**(1):82-99.

Douglas RG (1989). Antiviral agents. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, pp. 1182-1194.

GENE-TOX (2002). National Library of Medicine, National Institutes of Health. Available at: http://toxnet.nlm.nih.gov/. Access date: March 2002.

International Agency for Research on Cancer (IARC, 2000). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some Antiviral and Antineoplastic Drugs and Other Pharmaceutical Agents.* Volume 76, IARC, Lyon, France.

Mamber SW, Brookshire KW, Forenza S (1990). Induction of the SOS response in Escherichia coli by azidothymidine and dideoxynucleosides. *Antimicrob Agents Chemother* **34**(6):1237-43.

Nabhan C, Krett N, Gandhi V, Rosen S (2001), Gemcitabine in hematologic malignancies. *Curr Opin Oncol* **13**(6):514-521.

National Toxicology Program (NTP, 1999). *Toxicology and Carcinogenesis Studies of AZT (CAS No. 30516-87-1)* and AZT/α -interferon A/D in $B6C3F_1$ Mice (Gavage Studies). Technical Report No. 469. NIH Publication No. 99-3959. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

Olivero OA, Anderson LM, Diwan BA, Haines DC, Harbaugh SW, Moskal TJ, Jones AB, Rice JM, Riggs CW, Logsdon D, Yuspa SH, Poirier MC (1997). Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. *J Natl Cancer Inst* **89**(21):1602-1608.

Physicians' Desk Reference (PDR, 2000). Product information on CYTOSAR-U® (cytarabine); VIROPTIC® (trifluridine); GEMZAR® (gemicitabine); VIRAZOLE® (ribavirin); FLUDARA® (fludarabine); EPIVIR® (lamivudine); ZERIT® (stavidine); NIPENT® (pentostatin). 54th Edition. Medical Economics Company, Inc. Montvale, NJ.

Phillips MD, Nascimbeni B, Tice RR, Shelby MD (1991). Induction of micronuclei in mouse bone marrow cells: an evaluation of nucleoside analogues used in the treatment of AIDS. *Environ Mol Mutagen* **18**(3):168-83.

Rao GN, Collins BJ, Giles HD, Heath JE, Foley JF, May RD *et al.* (1996). Carcinogenicity of 2',3'-dideoxycytidine in mice. *Cancer Res* **56**(20):4666-72.

Sanders VM, Elwell MR, Heath JE, Collins BJ, Dunnick JK, Rao GN *et al.* (1995). Induction of thymic lymphoma in mice administered the dideoxynucleoside ddC. *Fundam Appl Toxicol* **27**(2):263-9.

Simpson MV, Chin CD, Keilbaugh SA, Lin TS, Prusoff WH (1989). Studies on the inhibition of mitochondrial DNA replication by 3'-azido- 3'-deoxythymidine and other dideoxynucleoside analogs which inhibit HIV- 1 replication. *Biochem Pharmacol* **38**(7):1033-6.