Takayama et al, 1989

Guidelines/Criteria	
Reference:	Takayama S, Hasegawa H, Ohgaki H. 1989. Combination effects of forty carcinogens administered at low doses to male rats. Jpn J Cancer Res 80:732-736.
In vivo **Study Type**	
Route of Administration	Dietary
Species & age of animals	F344 male rats; 6 weeks old at study start
Study Duration	102 weeks
Type of Mixture	
Binary	
>2 components	40 carcinogens
Similar acting or dissimilar	Not specified
What Mode of Action was investigated?	carcinogenicity
Parameters/End points Measured	
Target organs/Critical effects	Target sites of the 40 carcinogens included, liver, thyroid, urinary bladder, skin, Zymbal's gland, and 20 carcinogens exhibited two or more target sites.
Pharmacological changes or adverse effects	adverse
Individual Components	
Characterisation of individual compounds	40-component mixture consisting of:
Name, exact chemical name, CAS no.	Acetamide; 3-amino-9-ethylcarbazole HCl; 4-Amino-2-nitrophenol; 2-amino-5-nitrothiazole; 2-Aminoanthraquinone; aniline HCl; Anisidine HCl; Azobenzene; p-Benzoquinone dioxime; 4-Chloro-o-phenylenediamine; p-Chloroaniline; Clofibrate; p-Cresidine; Cupferron; Dapsone; 2,4-Diaminoanisol sulphate; 4,4'-Diaminodiphenyl ether; 2,4-Diaminotoluene; N,N'-Diethylthiourea; 2,4-Dinitrotoluene; Hydrazobenzene; Michler's ketone; Nafenopin; Nitriloacetic acid trisodium salt I; 5-Nitro-o-ansidine; 5-Nitroacenaphthene; N-Nitrosodiphenylamine; Reserpine; 4,4'-Thioaniline; o-Toluidine HCl; 2,3,6-Trichlorophenol; tris(2,3-Dibromopropyl)phosphate; 2-Amino-1,4-dimethyl-5H-pyridol[4,3-b]-indole; 3-Amino-1-methyl-5H-pyridol[4,3-b]indole; 2-Amino-6-methyldipyridol[1,2-a:3',2'-d]-imidazole; 2-Aminodipyridol[1,2-a:3',2'-d]-imidazole; 2-Amino-3-methylimidazo[4,5-f]quinolone; N-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide; 2-Acetylaminofluorene; 3'-Methyl-4-dimethylaminoazobenzene CAS Numbers not cited in paper.
Were dose responses established for individual components?	No. Choice of chemicals based on data in other publications.
Were no effect levels established?	Not in this publication
Were doses below the NO(A)ELs investigated?	Not clear
Mixtures Investigated	
Number of dose levels	One
How does the mixture make-up compare to individual components? (e.g. low dose) equivalents used?)	Each carcinogen was present in the mixture at 1/50th of its TD50 (tumorigenic dose causing tumours in 50% of treated F344 rats), as established in the reference publications.
No. of technical replicates per exposure condition (*in vitro*)	
No. of animals per dose group (*in vivo*)	30 per dose group
Observations/Findings	Despite the mixture containing eight urinary bladder carcinogens, there were no treatment-related changes in tumour incidence in this tissue. Of the other target organs examined, only the liver and thyroid revealed statistically significant increases in preneoplastic and neoplastic lesions: markedly increased incidence of neoplastic nodules in livers of treated rats, and combined increased incidence of follicular cell adenomas (n = 2) and follicular cell carcinomas (n = 3) of the thyroid. The authors conclude that, in the absence of data on the individual carcinogen tested at the dose present in the mixture, it is not possible to conclude whether the effects on the liver and thyroid were a result of synergistic or additive effects.
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Increased incidence of preneoplastic and neoplastic changes in liver and thyroid of treated animals. However, no conclusion can be derived concerning additivity, etc. As proposed by the authors, having data on individual substances may have allowed conclusions to be drawn.