Guidelines/Criteria	
Reference:	Ito N, Hagiwara A, Tamano S, Futacuchi M, Imaida K, Shirai T. 1996. Effects of pesticide mixtures at the acceptable daily intake levels on rat carcinogenesis. Food Chem Toxicol 34:1091-1096.
***In vivo* Study Type**	
Experiment 1	
Route of Administration	in the diet
Species & age of animals	male F344 rats, 6 week old
Study Duration	eight weeks (six weeks of treatment with test compounds)
Experiment 2	
Route of Administration	in the diet
Species & age of animals	male F344 rats, 6 week old
Study Duration	28 weeks (4 weeks of initiation and 24 weeks of treatment)
Type of Mixture	
Binary	
>2 components	**Exp. 1.** 20 pesticides mainly organophosphates ---- not considered here ---------- **Exp. 2.** 40 compounds of high production volume, 20 compounds with reported or suspected carcinogenicity, capatafol as positive control
Similar acting or dissimilar	not known, most likely dissimilar
What Mode of Action was investigated?	carcinogenicity
Parameters/End points Measured	
Target organs/Critical effects	liver, GST-P-positive liver foci in diethylnitrosamine- (200 mg/kg i.p.) and non-initiated rats (with partial hepatectomy after 3 weeks) - Experiment 1: reported in detail in Ito et al. (1995) Fd Chem Toxicol 33, 159-163 - evaluated separately, not considered here medium term multi-organ bioassay (DMBDD initiation during first 4 weeks), no initiation groups: vehicle only during first 4 weeks
Pharmacological changes or adverse effects	GST P positive liver foci as early marker of tumour development (exp. 1) - GST P positive liver foci and tumours (exp. 2)
Individual Components	
Characterisation of individual compounds	
Name, exact chemical name, CAS no.	40 pesticide mixture: acephate, bendicarb, bensulide, bentazone, chinomethionat, chlorobenzilate, chlorpropham, chlorpyriphos, clofentezine, cyfluthrin, cyhalothrin, cypermethrin, diflubenzuron, fenarimol, fenbutanatin oxide, fenvalerate, flucythrinate, flutolanil, glyphosate, imazalil, malathion, maneb, mepiquat chloride, metalaxyl, metolachlor, metribuzin, myclobutanil, oxamyl, pendimethalin, permethrin, pirimiphosmethyl, propiconazole, pyrifenox, quinclorac, sethoxidim, thiobencarb, triadimefon, trichlorfon, vinclozolin, zineb. 20 pesticide mixture: acephate, amitraz, captafol, clofentezine, cypermethrin, 2,4-D, dichlorvos, dichlobenil, dicofol, foset, glyphosate, mancozeb, maneb, mefolachlor, permethrin, phosmet, propiconazole, propoxur, triadimefon, trifluralin. Captafol (1500 mg/kg) as positive control. Purities or CAS numbers were not given.

Were dose responses established for individual components?	no
Were no effect levels established?	no, the work is based on previously established ADI levels
Were doses below the NO(A)ELs investigated?	yes - with respect to conventional NOAELs, no - with respect to the animal models used
Mixtures Investigated	
Number of dose levels	one
How does the mixture make-up compare to individual components? (e.g. low dose) equivalents used?)	each compound at the respective ADI
No. of technical replicates per exposure condition (*in vitro*)	
No. of animals per dose group (*in vivo*)	19-20 for DNBDD-initiated rats, not clear for non-initiated rats (20 ?)
Observations/Findings	In DMBDD-initiated rats bodyweight was slightly increased in the 40 pesticide mixture group and slightly decreased in the captafol group. Relative liver and kidney weights were increased in the captafol group. In DMBDD-initiated animals only captafol increased the number or area of GST-P-positive liver foci. In the various organs, only captafol induced tumours, namely thyroid follicular adenoma. In the non-initiated animals neither preneoplastic nor neoplastic lesions were observed. (A no initiation/no treatment group was not run.)
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Unclear animal number for non-initiated animals. No dose responses established for individual compounds in the models used, work is based on previously established ADIs (not established in the liver DMBDD model). Not in line with the Task Force's criteria (no testing of single compounds in the models used, no NOAEL established in the model), but potentially useful, since a large number of compounds was tested in a sensitive model at their respective ADIs.