Extract from the **Assessment Report (May 2009) prepared by RMS UK** in the context of Annex I renewal under the PPP directive

The data were extracted from the report disseminated by EFSA (http://dar.efsa.europa.eu/dar-web/provision)

Further data and assessments (e.g., CA report) were prepared in the context of the BPR assessment of Azoxystrobin, which are already available to ECHA. However, they are currently not publically available.

B.6.4 Genotoxicity studies (IIA 5.4)

B.6.4.1 Genotoxicity *in vitro* (IIA 5.4.1)

B.6.4.1.1 Gene mutation in bacteria

Study	ICIA5504: An evaluation of mutagenic potential using *Salmonella typhimurium* and *Escherichia coli.*
Reference	Callander R D (1992)
Date performed	July 1992
Test facility	Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK
Report reference	Report No. CTL/P/3790.
Guideline(s)	OECD 471; EC B.14
Deviations from the guideline	None
GLP	Yes
Test material	batch P39, purity 97.2 %
Study acceptable	Yes

Material and methods:

Test system: The study was conducted using *Salmonella typhimurium* strains TA1535, Ta1537, TA98 and TA100, and *Escherichia coli* strains WP2 (pKM101) and WP2 uvrA (pKM101). Six test concentrations of azoxystrobin (batch P39, purity 97.2 %) ranging from 100 - 5000 µg/plate were tested both in the presence and absence of an auxiliary metabolic activation system (S9-mix) derived from the livers of phenobarbital/β-naphthaflavone-induced male [redacted] rats. Three plates were tested per concentration, strain and S9-mix condition. Appropriate positive and solvent controls were included for each strain and S9-mix condition. Dimethylsulfoxide (DMSO) was used as the solvent for the test compound and for most of the positive control substances and served as negative control. The compound was assayed in two independent experiments. The incubation period for each experiment was 3 days (at 37°C). The first S9-mix experiment and both experiments without activation were conducted using the standard Plate Incorporation assay protocol. The second +S9-mix experiment was conducted using a Pre-Incubation (37°C, 60 minutes) protocol.
Evaluation criteria: A response in a (valid) individual experiment was considered positive when a) a statistically significant dose-related increase in the mean number of revertant colonies is obtained and/or b) a two-fold or greater and statistically significant increase in the mean number of revertant colonies over that observed for the concurrent solvent control plates is observed at at least one dose level.
Statistics: An assessment of statistical significance was carried out using a one-tailed Student´s t-test.

Findings:

Precipitation was observed at the highest concentration and in one experiment also at a concentration of 2500 µg/plate. No reproducible, significant increases in revertant colony numbers were observed in any strain, either in the presence or absence of S9-mix. In each case, the positive control chemicals gave the expected responses indicating the sensitivity of the assay and the metabolic competence of the S9-mix.

Conclusion:

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Under the conditions of assay used in this study, the test substance gave a negative, ie, non-mutagenic response.

Callander (1992)

B.6.4.1.2 Gene mutation in mammalian cells

Study	ICIA5504: Assessment of mutagenic potential using L5178Y mouse lymphoma cells.
Reference	Callander R D & Clay P (1993)
Date performed	January 1993 – March 1993
Test facility	Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK
Report reference	Report No. CTL/P/3963
Guideline(s)	OECD 476
Deviations from the guideline	None
GLP	Yes
Test material	batch P49, purity 96.2 %
Study acceptable	Yes

Material and methods:

Test system: The study was conducted using L5178Y mouse lymphoma cells, screening for forward mutations at the TK locus with trifluorothymidine as the selective agent, both in the presence and absence of a liver S9 preparation derived from phenobarbital/β-naphthaflavone-induced male [redacted] rats. For testing, azoxystrobin (batch P49, purity 96.2 %) was diluted in DMSO which was also used as the vehicle for positive control substances and as negative (solvent) control. Positive controls were the direct acting mutagen ethyl methanesulphonate (EMS) and N-nitrosodimethylamine (NDMA) which requires metabolic activation. Three independent experiments were conducted in the presence and absence of metabolic activation (S9-mix). Azoxystrobin was tested at concentrations ranging from 8 µg/ml to 60 µg/ml in the first experiment, 34 µg/ml to 80 µg/ml in the second and 26 µg/ml to 80 µg/ml in the third trial. In each case, testing was performed both in the presence and absence of S9-mix. The concentrations had been determined on the basis of a preliminary dose-ranging study. Each experiment was conducted in Microtitre™ plates, using duplicate cultures per concentration. The treatment period was 4 hours and the expression period was 3 days.
Evaluation criteria: A positive response in a (valid) experiment is recorded when statistically significant and dose-related increases in mutant frequency are observed across a range of concentrations including dosages with no or only little toxicity (cell survival >10 %). The absolute number of mutants must exceed the concurrent negative control values. This response must be reproducible in an independent experiment.
Statistics: Logit regression was applied for data consideration. In addition, tests for trend and intergroup comparisons in log mutant frequency were performed.

Findings:

Azoxystrobin generally produced equivalent levels of toxicity in the presence and absence of S9-mix down to approximately 30 % survival at the maximum concentration in the first experiment (60 µg/ml) and approximately 10 % at the maximum concentrations evaluated in the second and third experiments (80 µg/ml). Dose related toxicity was seen in all experiments. The spontaneous

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mutant frequency (solvent control) in the absence of S9-mix in the second experiment was outside the acceptable range for this test system and the data were not evaluated or reported. Small but statistically significant and reproducible increases in mutant frequency (in some cases associated with increases in absolute mutant numbers) were seen at several concentrations tested with and without metabolic activation. All experiments evaluated for mutation induction gave statistically significant linear trends with concentration.

The positive controls induced statistically significant increases in mutant frequency in all experiments demonstrating that the assay was performing satisfactorily.

An examination of the data with respect to the occurrence of large or small mutant colonies showed that the increases in mutant frequency were mainly due to increases in the numbers of small colonies (i.e., mutant clones with slow growth kinetics). However, this is not true for all dose levels in all experiments. Results obtained in the third experiment with and without S9-mix are tabulated below (Table B6.4.1.2-1).

Table B.5.4.1.2-1: Mouse lymphoma cell assay with azoxystrobin; Mutant frequency (3rd experiment)

Azoxystrobin concentration (µg/ml)	S9-mix	Survival (%)	Mutant frequency ($x10^{-4}$)	Small colonies (total per culture)	Large colonies (total per culture)
80	-	12	6.1**	72, 63	19, 33
64	-	18	1.9**	63, 65	24, 31
51	-	19	2.9**	90, 83	38, 57
41	-	24	2.1**	79, 80	44, 49
33	-	30	1.4	58, 40	30, 26
26	-	37	1.7*	58, 73	43, 44
Negative control DMSO	-	100	1.2	32, 38	42, 36
Positive control EMS (750 µg/ml)	-	38	25.1**	68, 54	275, 268
80	+	8	3.6**	139, 153	70, 118
64	+	21	2.4**	105, 120	53, 87
51	+	22	2.5**	101, 80	67, 72
41	+	29	4.9**	72, 77	157, 193
33	+	38	1.7	56, 48	71, 36
26	+	48	1.7	71, 68	81, 39
Negative control DMSO	+	100	1.3	53, 33	57, 60
Positive control NDMA (600 µg/ml)	+	26	26.2**	200, 234	122, 82

statistically significant * $p<0.05$, ** $p<0.01$

Conclusion:

Under the conditions of this assay, azoxystrobin was genotoxic to L5178Y TK+/- cells in both the presence and absence of S9-mix. Findings suggest that this was mainly due to an increase in the number of small mutant colonies in the treated cultures. It is generally considered that an increase in large mutant colonies may reflect gene mutation events while an increase in small mutant colonies may reflect clastogenic events affecting not only the TK-locus but also additional genes (Applegate *et al.*, 1990). Since the induction of small mutant colonies has been shown to be

associated with gross chromosomal damage, this assay provides evidence of a clastogenic potential of the test substance at least *in vitro*.

Callander & Clay (1993)

B.6.4.1.3 Cytogenetic assay in mammalian cells

Study	ICIA5504: An evaluation in the *in vitro* cytogenetic assay in human lymphocytes.
Reference	Fox D A & Mackay J M (1992)
Date performed	September 1991 – November 1991
Test facility	Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK
Report reference	Report No. CTL/P/3607
Guideline(s)	OECD 473; EC B.10
Deviations from the guideline	Exposure period with S9 only 3 hours.
GLP	Yes
Test material	batch P49, purity 96.2 %
Study acceptable	Yes

Material and methods:

Acceptance: The study is considered acceptable.
Test system: The test was carried out using lymphocytes from two healthy non-smoking human donors (one male and one female) in the presence and absence of an auxiliary metabolic activation system (S9-mix, obtained from the livers of Aroclor 1254-induced CD rats). Duplicate cultures were initiated in supplemented RPMI-1640 culture medium and incubated at 37□ C for 48 hours before they were exposed to azoxystrobin (batch P32, purity 95.2 %). A range of eight concentrations of between 0.5 and 50 µg/ml in the absence of S9-mix and between 1 and 300 µg/ml in the presence of S9-mix (200 µl of a 1:1 mix of S9 and co-factor) were tested. These concentration levels were selected on the basis of a preliminary range-finding cytotoxicity test. The test compound was dissolved in DMSO which was also used as negative (solvent) control. The positive controls, mitomycin C and cyclophosphamide, were administered at concentrations of 0.2 µg/ml and 50 ug/ml (diluted in sterile double deionised water) in the absence and presence of S9-mix, respectively. In the presence of S9-mix, cultures were treated for a period of 3 hours, after which the culture medium was removed by centrifugation and replaced with fresh supplemented RPMI-1640 medium. In the absence of S9-mix, the cultures were treated for a period of 24 hours. Thereafter, cultures from both donors were maintained at 37□ C until the end of the 72 hour growth period. In addition, cultures from the female donor were also harvested at the later time of 96 hours after culture initiation. Two hours prior to harvesting at 72 or 96 hours, the cultures were treated with colcemid to arrest dividing lymphocytes in metaphase. At harvest, the culture medium was removed following centrifugation, the cells were treated with a hypotonic solution (0.075M KCl) and fixed in methanol/acetic acid fixative (3:1 v/v). Slides were prepared for each culture by dropping cell suspension onto clean, dry labelled microscope slides. The slides were air dried, stained in a filtered 10 % solution of Giemsa stain in buffered (pH 6.8) double deionised water, rinsed in water, air-dried and mounted with coverslips in DPX.
The mitotic index was determined by examining 1,000 lymphocytes per culture and calculating the percentage of cells in metaphase. This was done in cultures treated with azoxystrobin and the relevant solvent and positive control cultures. In the absence of S9-mix, duplicate cultures treated with azoxystrobin at concentrations of 1, 10 and 20 µg/ml for the male donor or 5, 20 and 50 µg/ml for the female donor, were selected for chromosomal aberration analysis along with

duplicate solvent control cultures and a single positive control culture at the 72 hour sampling time. In the presence of S9-mix, duplicate cultures from both donors treated with azoxystrobin at concentrations of 25, 100 and 200 µg/ml were selected for chromosomal aberration analysis along with appropriate control cultures at the 72 hour sampling time. In each case, the highest concentration of azoxystrobin selected for chromosomal aberration analysis was based on a significant reduction in mean mitotic activity compared to the solvent control cultures and the suitability of the metaphase preparations for analysis. In addition, cultures from the female donor treated at 20 ug/ml in the absence of S9-mix and 200 ug/ml in the presence of S9-mix were selected for analysis at the 96 hour sampling time along with the appropriate solvent control cultures. The slides were coded to avoid observer bias and 100 cells in metaphase per culture were analysed for the incidence of structural chromosomal aberrations.
Statistics: Fisher's exact test (one sided) was applied to compare data from each of the treatment groups to the appropriate solvent control values.

Findings:

Significant reductions in mean mitotic activity, compared to the solvent control cultures, were observed following the 72 hour expression period for both the male (68 % without S9-mix; 64 % with S9-mix) and female (78 % without S9-mix; 71 % with S9-mix) donor cultures treated with the highest concentrations of azoxystrobin selected for chromosomal aberration analysis.
At the 72 hour sampling time, statistically and biologically significant increases in the percentage of aberrant cells, compared to the solvent control values, were recorded in cultures treated with azoxystrobin in the absence of S9-mix at concentrations of 20 µg/ml in the male donor and 5, 20 and 50 µg/ml in the female donor (see Table B.6.4.1.3-1).

Table B6.4.1.3-1: Cytogenetic study in human lymphocytes; Mitotic index and chromosome aberration frequency in the absence of S9-mix, 72 hour sampling

Treatment	Mean mitotic index (%)	Mean % aberrant cells excluding gaps	Aberrations per cell excluding gaps
Donor 1 (male)			
DMSO (5 µl/ml)	7.3	0.00	0.000
Mitomycin C (0.2 µg/ml)	5.8	43.00**	0.690
Azoxystrobin 20 µg/ml	2.3	4.50**	0.060
Azoxystrobin 10 µg/ml	3.3	2.00	0.020
Azoxystrobin 1 µg/ml	5.5	1.00	0.015
Donor 2 (female)			
DMSO (5 µl/ml)	7.3	1.00	0.015
Mitomycin C (0.2 µg/ml)	5.1	59.00**	1.270
Azoxystrobin 50 µg/ml	1.6	6.00**	0.060
Azoxystrobin 20 µg/ml	1.7	8.00**	0.095
Azoxystrobin 5 µg/ml	8.0	4.50**	0.045

statistically significant * $p<0.05$, ** $p<0.01$

Statistically and biologically significant increases in the percentage of aberrant cells, compared to the solvent control values, were recorded in cultures treated with azoxystrobin in the presence of S9-mix at a concentration of 200 µg/ml in both the male and female donor cultures (see Table B.6.4.1.3-2). A small but statistically significant increase was also noted in the male donor cultures treated at 100 µg/ml.
In both experiments, azoxystrobin concentrations causing a marked reduction in mitosis rate also induced a considerably higher frequency of chromosomal aberrations.

No statistically or biologically significant increases in the percentage of aberrant cells and no reductions in mitotic index were recorded at the 96 hour sampling time.
The sensitivity of the test system and the metabolic activity of the S9-mix employed were clearly demonstrated by the marked increases in the frequencies of chromosomal aberrations induced by the positive control agents mitomycin C and cyclophosphamide.

Table B.6.4.1.3-2: Cytogenetic study in human lymphocytes; Mitotic index and chromosome aberration frequency in the presence of S9-mix, 72 hour sampling

Treatment	Mean mitotic index (%)	Mean % aberrant cells excluding gaps	Aberrations per cell excluding gaps
Donor 1 (male)			
DMSO (5 µl/ml)	4.5	0.00	0.000
Cyclophosphamide (50 µg/ml)	4.4	20.00**	0.340
Azoxystrobin 200 µg/ml	1.6	11.50**	0.185
Azoxystrobin 100 µg/ml	3.8	2.50*	0.025
Azoxystrobin 25 µg/ml	6.0	1.50	0.020
Donor 2 (female)			
DMSO (5 µl/ml)	4.9	0.50	0.005
Cyclophosphamide (50 µg/ml)	2.6	18.00**	0.210
Azoxystrobin 200 µg/ml	1.4	6.50**	0.070
Azoxystrobin 100 mg/ml	3.0	1.00	0.010
Azoxystrobin 25 µg/ml	4.2	2.50	0.025

statistically significant * $p<0.05$, ** $p<0.01$

Conclusion:

Under the conditions of this assay, azoxystrobin is considered to be clastogenic to cultured human lymphocytes *in vitro* in the presence and absence of S9-mix. In addition, the test compound caused dose-related reductions in mitotic activity at concentrations where increased aberration rates were seen.

(Fox & Mackay (1992))

B.6.4.2 Genotoxicity *in vivo* (IIA 5.4.2)

B.6.4.2.1 Mouse bone marrow micronucleus assay

Study	E5504: An evaluation in the *mouse micronucleus assay*
Reference	Jones K & Mackay J M (1992)
Date performed	December 1991
Test facility	[redacted]
Report reference	Report No. [redacted]P/3647
Guideline(s)	OECD 474; EC B.12
Deviations from the guideline	None
GLP	Yes
Test material	batch P39, purity 97.2 %
Study acceptable	Yes

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Material and methods:

Test system: C57BL/6JfBL10/Alpk mice (9-12 weeks old; source: [redacted]), were given a single oral dose of either corn oil (vehicle control), cyclophosphamide (positive control, 65 mg/kg bw) or azoxystrobin (batch P39, purity 97.2 %) at 5000 mg/kg bw (dissolved in corn oil). This dose was considered the limit dose for this assay since no adverse reactions to treatment at this dose level had been observed over a four day observation period in a preliminary experiment. Mice of the test compound-treated and vehicle control groups were killed by cervical dislocation 24 and 48 hours after dosing. Groups consisted of five male and five female mice per sampling time each. Positive control animals (five per sex) were sacrificed at 24 hours after treatment only.
Paintbrush smears of the bone marrow from the femur were prepared on clean, labelled microscope slides. The slides were allowed to dry and were stained with polychrome methylene blue and eosin, mounted with coverslips in DPX, coded and analysed blind.
One thousand polychromatic erythrocytes per slide were examined for the presence of micronuclei. One thousand erythrocytes per animal were examined to measure the ratio of polychromatic to normochromatic erythrocytes, as evidence of cytotoxicity to the target tissue may be manifest in alterations to the ratio of these cells in the bone marrow. Extended analysis of an additional one thousand polychromatic erythrocytes per animal for the presence of micronuclei was conducted using areas of the slides which were different from those originally analysed.
Statistics: Analysis of variance and one-sided Student's t-test were used.

Findings:

Adverse reactions to treatment were observed for females dosed with azoxystrobin. Clinical signs noted included subdued behaviour, tiptoe gait, piloerection, signs of diarrhoea and signs of urinary incontinence on the day of dosing. No adverse reactions were noted on subsequent days.
No statistically or biologically significant increases in the incidence of micronucleated polychromatic erythrocytes, over vehicle control values, were seen at either of the sampling times investigated when the original and extended counts were considered separately or following combination of the counts.
Comparison of the percentage of polychromatic erythrocytes showed a statistically significant reduction, compared to the vehicle control values, for azoxystrobin-treated males at the 48 hour sampling time. This indicates that azoxystrobin, or a metabolite, may have induced a cytotoxic response in the bone marrow resulting in a depression in cell proliferation.
The positive control material, cyclophosphamide, induced statistically significant and biologically meaningful increases in micronucleated polychromatic erythrocytes, compared to the vehicle control values, thus demonstrating the sensitivity of the test system to a known clastogen.

Conclusion:

Under the conditions of the test, azoxystrobin is not clastogenic in the mouse bone marrow micronucleus test. There was evidence of cytotoxicity in the bone marrow indicating that this tissue has been actually reached by the test material or its metabolites.

(Jones & Mackay (1992))

B.6.4.2.2 DNA damage and repair (UDS) assay in rat hepatocytes

Study	E5504: Assessment of the induction of unscheduled DNA synthesis in rat hepatocytes *in vivo*.

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Reference	Lane M P and Kennelly J C (1992)
Date performed	January 1992 – February 1992
Test facility	[redacted]
Report reference	Report No. [redacted]/P/3682
Guideline(s)	None existing at time of study performance. OECD 486 subsequent
Deviations from the guideline	Broadly in line with OED 486
GLP	Yes
Test material	batch P39, purity 97.2 %
Study acceptable	Yes

Material and methods:

Test method: No specific guideline is currently available for *in vivo* mammalian liver unscheduled DNA synthesis (UDS) studies. According to the applicant, the acceptance criteria were modified from a draft OECD guideline in preparation.
GLP: Yes.
Acceptance: The study is considered acceptable.
Test system: Male young adult Alpk:APfSD rats (source: [redacted]) were given a single dose of 1250 or 2000 mg/kg bw of azoxystrobin (batch P39, purity 97.2 %) by oral gavage. Dose levels had been selected on the basis of a preliminary toxicity test.
Animals were killed 2 or 16 hours post-dose and hepatocytes were isolated by a collagenase perfusion technique. Four independent experiments were conducted to give a total of 5 azoxystrobin-treated rats per dose level/time point. Two vehicle control (corn oil) and at least two positive control animals were also included in each trial. Positive control substances were 2-acetylaminofluorene (2-AAF) for the 16 hour treatments and N-nitrosodimethylamine (NDMA) for the 2 hour treatments. However, not all of these control rats were scored for induction of UDS. A third positive control substance, 1,2-dimethylhydrazine dihydrochloride (DMH.2HCl) was dosed in experiments 1, 2 and 3 to single animals which were all evaluated for UDS then.
At least three hepatocyte cultures per animal were exposed to [^{3}H]-thymidine for 4 hours. Cultures were washed and incubated overnight with medium containing an excess of unlabelled thymidine. Cells were washed, fixed and coverslips mounted onto microscope slides for autoradiography. These slides were coated with photographic emulsion and left for 14 days at 4°C in the dark. Thereafter, the emulsion was developed and the cells were stained. The preparations were examined and the amount of radiolabel in the nucleus [N] compared with that of the most heavily labelled area of cytoplasm [C]. The value [N-C], the net nuclear grain count, is an index of unscheduled DNA synthesis (UDS). Mean [N-C] values were determined for 30 cells/slide, two slides per animal.
Evaluation criteria: To be considered positive, a test treatment should result in a mean net nuclear grain count of 0 or greater in a treated animal with such a response being reproduced in animals treated concurrently and in an independent repeat experiment.

Findings:

No signs of acute toxicity were noted in any of the azoxystrobin-treated rats. Furthermore, there were no apparent signs of excessive cytotoxicity in the hepatocyte cultures. Therefore, hepatocytes obtained from rats exposed at both dose levels could be assessed for the induction of UDS.
Determination of the mean net nuclear grain count and percentage of cells in repair showed that azoxystrobin did not induce DNA repair, as measured by UDS, at either dose level or time point investigated.

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The positive control materials 2-acetylaminofluorene, N-nitroso-dimethylamine and 1,2-dimethylhydrazine dihydrochloride induced the expected levels of UDS, thus confirming the ability of the test system to detect chemically induced DNA repair.

Conclusion:

It is concluded that when tested up to the limit dose level of 2000 mg/kg bw, azoxystrobin did not induce unscheduled DNA synthesis indicative of compound-related DNA damage and repair in the rat liver under the conditions of this *in vivo*-assay.

(Lane & Kennelly (1992))

B.6.4.3 Summary of genotoxicity studies

Azoxystrobin has been evaluated in a range of genotoxicity assays, including endpoints of gene mutation, chromosomal damage and DNA repair. The results are summarised in Table B.6.4.3-1 below.

Azoxystrobin has been found to give a negative result in the Ames test and a weak positive response in two studies using mammalian cells *in vitro*. The latter findings suggest a clastogenic potential of the test substance *in vitro* as the increased occurrence of small colonies in the mouse lymphoma cell assay is considered indicative rather of chromosome aberrations than of point mutations.

In contrast, azoxystrobin has been shown to be negative in established *in vivo* assays for chromosomal damage (ie clastogenicity) and for general DNA damage at high dose levels of 2000 mg/kg bw or above. It should be taken into account that both *in vivo* tests performed are considered appropriate to detect clastogenic effects. It can be concluded, therefore, that the clastogenic effects seen *in vitro* are not expressed in the whole animal. Furthermore, chronic studies have not shown any evidence of carcinogenicity in the mouse and the rat when dosed for up to two years (see section B.6.5). Regarding the weight of evidence from all relevant studies, it is scientifically justified to consider azoxystrobin not to express genotoxicity *in vivo*.

Table B.6.4.3-1.x Summary of genotoxicity studies

Study	Test system	Result	Reference
In vitro			
Bacterial reverse mutation	*S. typhimurium* & *E. coli*	Negative	Callander, 1992
Mammalian cell gene mutation	Mouse lymphoma L5178Y cells	Positive at cytotoxic concentrations	Callander & Clay, 1993
Chromosome aberrations	Human lymphocytes	Positive	Fox & Mackay, 1992
In vivo			
Bone marrow micronucleus	C57BL mice	Negative	Jones & Mackay, 1992
DNA damage & repair (UDS)	Alpk:APfSD male rat hepatocytes	Negative	Lane & Kennelly, 1992