Regulatory Guideline studies to investigate developmental effects of glyphosate

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Fraunhofer
ITEM

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, route, duration	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Brooker *et al.*, 1991, TOX9552393; 206-Jak-25-1, 98.6%; Cheminova	Developmental, CD, gavage, d 6-15 p.c.	0, 300, 1000, 3500 mg/kg bw/d	Maternal & developmental: 300 mg/kg bw/d	Maternal & dev.: 1000 mg/kg bw/d	Maternal: slight bw gain↓, noisy respiration (2/25); Dev.: ossification↓, skeletal anomalies	Study acceptable; previous evaluation confirmed

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, route, duration	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Suresh, 1991, TOX9551105; FSG 03090 H/05. March 90, 96.8%; Feinchemie	Develop-mental, Wistar, gavage, d 6-15 p.c.	0, 1000 mg/kg bw/d	Maternal: 1000 mg/kg bw/d Dev. < 1000 mg/kg bw/d	Maternal: not established Dev.: 1000 mg/kg bw/d	Maternal: no effects; Dev.: ossi-fication↓	Study acceptable as limit-test; maternal NOAEL confirmed, dev. NOAEL (previously 1000 mg/kg bw/d) not confirmed

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, route, duration	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Tasker & Rodwell, 1980; TOX9552392; Batch not stated, 98.7%; Monsanto	Developmental, Charles River, gavage, d 6-19 p.c.	0, 300, 1000, 3500 mg/kg bw/d	Maternal&dev.: 1000 mg/kg bw/d	Maternal & dev. 3500 mg/kg bw/d	Maternal:mortality, soft stool, diarrhea, Dev.: bw↓, post implantation losses	Study acceptable; previous evaluation confirmed

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, route, duration	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Anonym (Antal?), 1981; TOX9650160; Batch not stated, purity 96.8%; Alkaloida	Develop-mental, CFY, diet, d 6-18 p.c.	Calculated to be 0, 22, 103, 544 mg/kg bw/d	Maternal & dev.: 544 mg/kg bw/d	Not established	No treatment related effects	Study supple-mentary; previuos evaluation confirmed

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, route, duration	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Anonym (Antal?), 1981; TOX9650160; Batch not stated, purity 96.8%; Alkaloida	Developmental, CFY, diet, d 6-18 p.c.	Calculated to be 0, 22, 103, 544 mg/kg bw/d	Maternal & dev.: 544 mg/kg bw/d	Not established	No treatment related effects	Study supplementary; previuos evaluation confirmed

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of RMS evaluation
Moxon, 1996; TOX2000-2001 and 2002 ASB2012-10080; Y04707/034, 95.6%; Syngenta	Developmental, Alpk (Wistar derived), gavage, d 7-16 p.c.	0, 250, 500, 1000 mg/kg bw/d	Maternal & dev.: 1000 mg/kg bw/d	Not established	None	Study acceptable: JMPR (2004, ASB2008-6266) evaluation confirmed

Rat

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of RMS evaluation
Hatakenaka, 1995 ASB2012-11497; 940908-1, 95.68%; Arysta	Develop-mental, CD (SD),, gavage, d 6-15 p.c.	0, 30, 300, 1000 mg/kg bw/d	Maternal&dev.: 300 mg/kg bw/d	Maternal& dev: 1000 mg/kg bw/d	Maternal: Loose stool Dev.: skeletal anomalies↑	Study acceptable

Rabbit

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Suresh *et al.*, 1993; TOX9551106; Batch 60, 96.8%; Feinchemie	Develop-mental, NZW rabbit, d 6-18 p.c., gavage	0, 20, 100, 500 mg/kg bw/d	Maternal: 20 mg/kg bw/d. dev.: 100 mg/kg bw/d	Maternal: 100 mg/kg bw/d; dev.: not established due to low number of foetuses	Maternal: mortality, soft/liquid stool; dev.: no clear-cut effects up to 100 mg/kg bw/d, high dose group excluded due to low number of foetuses/ litters	Study sup-plementa-ry, previous NOAELs confirmed

Foetal findings in the study by Suresh (1993)

Dose group (mg/kg bw/d)	0	20	100	500
Percentage of foetuses with 'dilated heart'	0.0	5.1*	5.2*	17.9*
No. affected/total number of foetuses examined	-	4/78	4/77	5/28
Litters affected/no. of litters	-	3/13	2/12	2/6
Foetuses with major visceral malformations	4/133	6/78	6/77	8/28
Percentage of foetuses with extra 13^{th} rib	0.0	1.3	2.6	3.6*

* statistically significant, $p \leq 0.05$

Mid & high dose: overt maternal toxicity incl. death
high embryonic loss

Rabbit

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Tasker *et al.*, 1980; TOX9552390; Lot XHJ-64, 98.7%; Monsanto	Develop-mental, Dutch Belted rabbit, d 6-27 p.c., gavage	0, 75, 175, 350 mg/kg bw/d	Maternal: 75 mg/kg bw/d, dev.: 175 mg/kg bw/d	Maternal: 175 mg/kg bw/d, dev.: not established due to low number of foetuses	Maternal: mortality, soft stool, Diarrhea; dev.: none	Study supple-mentary, previous maternal NOAEL confirmed, dev. NOAEL revised

Rabbit

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Brooker *et al.*, 1991; TOX9552391; 206-Jak-25-1, 98.6%; Cheminova	Develop-mental, NZW rabbit, d 7-19 p.c., gavage	0, 50, 150, 450 mg/kg bw/d	Maternal: 50 mg/kg bw/d, dev.: 150 mg/kg bw/d	Maternal: 150 mg/kg bw/d, dev.: 450 mg/kg bw/d	Maternal: GI-tract, food & bw gain ↓: dev.: late embryonic death, post implanta-tion loss, cardiac malforma-tions*	Study acceptable, previous evaluation partly confirmed

* observed at excessive maternally toxic dose level

Rabbit, BROOKER et al., 1991

High dose: one maternal death

Elevated post-implantation loss in all treated groups
(upper end of hcd), no dose response

Ventricular septal defects:
1; 1; 1; 4/4

Rabbit

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of re-evaluation
Bhide & Patil, 1989; TOX9551960; Lot 38, 95%; Barclay, Luxan	Devleop-mental, NZW rabbit, d 6-18 p.c., gavage	0, 125, 250, 500 mg/kg bw/d	Maternal& dev.: 250 mg/kg bw/d	Maternal&dev 500 mg/kg bw/d	Maternal: food, bw↓, abortion; Dev.: dead foetuses, malforma-tions (external, visceral & skeletal)	Study supple-mentary due ot severe reporting deficien-cies, previous NOAELs confirmed

Rabbit

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of RMS evaluation
Hojo, 1995, ASB2012-11498; T-041209, 97.56%; Arysta	Develop-mental, Japanese White rabbits (Kbl:JW), d 6-18 p.c., gavage	0, 10, 100, 300 mg/kg bw/d	Maternal: 100 mg/kg bw/d, Developmental: 300 mg/kg bw/d	Maternal: 300 mg/kg bw/d, Developmen-tal: not Established	Maternal: Loose stool, abortion, 1 doe died; Dev.: none	Study acceptable

Rabbit

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of RMS evaluation
Coles & Doleman, 1996; ASB2012-11499; H95D161A, 95.3%; Nufarm	Develop-mental, NZW rabbit, d 7-19 p.c., gavage	0, 50, 200, 400 mg/kg bw/d	Maternal & dev.: 50 mg/kg bw/d	Maternal& dev.: 200 mg/kg bw/d	Maternal: bw gain ↓, Dev.: post-implanta-tion loss	Study acceptable

Rabbit

Reference; Study identification; Batch, purity; Owner	Study type, strain, duration, route	Dose levels	NO(A)EL	LO(A)EL	Targets/ Main effects	Outcome of RMS evaluation
Moxon, 1996; TOX2000-2002; Y04704/034, 95.6%; Syngenta	Develop-mental, NZW rabbit, d 8-20 p.c., gavage	0, 100, 175, 300 mg/kg bw/d	Maternal: 100 mg/kg bw/d, Dev.:175 mg/kg bw/d	Maternal: 175 mg/kg bw/d Dev.: 300 mg/kg bw/d	Maternal: food, bw gain ↓, clinical signs, dev.: foetal wt & ossi-fication ↓	Study acceptable, 2004 JMPR evaluation confirmed

Summary:

7 studies in rats, no specific concern

7 studies in rabbits, two in in the grey zone

Does this justify classification and labelling:

cat. 1b / 2 ?

cat. 2 / 3

"... misconception that materials can be categorised absolutely as teratogens or nonteratogens, a belief that is contrary to one of the basic principles of teratology, namely, that any material may be teratogenic if given to the right species at the right time at the right dosage."

A. K. Palmer, 1980