

Table 5: In Vivo Studies

Test Animal	Test Substance	Dose	Frequency	Estimated equivalent dose of dry weight comfrey for 60kg human ^a	Results	Ref
Male Rats 1-1.5 months old	Symphytine (i.p.)	13mg/kg	twice weekly for 4 weeks and then once a week for 52 weeks. (Experiment ran 21 months)	7 - 1040kg leaf ^b or 0.35 - 52kg leaf ^c	liver cell adenoma: 1 rat out of 20 herangioendothelial sarcomas of the liver: 3 rats out of 20 megalocytosis and proliferation of oval cells and endothelium of the sinusoids	[81]
Male rats (n=3)	Echimidine	20mg/kg	thrice weekly for 136 days	dose is about 3 to 4.5 times dose reported for symphytine study above ^d	limited megalocytosis of the midzone and periphery of the lobule	[85]
Male and Female rats 1-1.5 months old	Leaf	% of diet 33% 33% 16% 8%	for 480 days for 600 days for 600 days for 600days	0.5kg (1lbs) ^e 0.24kg (0.5lb) 0.12kg (0.25lb)	incidence of liver tumors ^f 26% 58% 33% 4%	[89]
	Root	% of diet 8% 4%/2%/1% 4%/0.5%/0% 2%/0.5%/0% 1%/0.5%/0%	variable time courses, >179 days with first diet composition	0.12kg (4oz) 0.06kg (2 oz) 0.03kg (1 oz) 0.02kg (0.5 oz)	incidence of liver tumors ^f 86% 43% 33% 43% 80%	
Male Rats (140g)	<i>Symphytum</i> leaf	% of diet 5% 10% 30%	21 days	0.3kg (0.67 lbs) 0.6kg (1.3lbs) 1.8kg (4lbs)	at 30% comfrey there was a significant decrease in daily weight gain at 10% and 30% comfrey (and 30% alfalfa) significant increase in Aminopyrine-N-demethylase activity. No changes in Glutathione S-transferase or Epoxide hydrolase at any feeding levels.	[90]
Rats 2 weeks old	Total Symphytum PA (i.p.)	284 mg/kg	once	19kg -130g leaf (42lbs - 4.5oz) or 2.8kg - 34g root (6lbs - 1.2 oz)	peracute (non-hepatic) deaths	[65]
		142 mg/kg	once	9.5kg - 65g leaf (21 lbs - 2.2oz) or 1.4kg - 17g root (3lbs - 0.6oz)	Temporary distress, no histological liver damage evident when rats killed 4 weeks later.	

Test Animal	Test Substance	Dose	Frequency	Estimated equivalent dose of dry weight comfrey for 60kg human ^a	Results	Ref
Male and female rats 2 weeks old	Total Symphytum PA (i.p.)	71 mg/kg	thrice weekly until death at 3-4 weeks	4.7kg - 32g leaf (10lbs - 1oz) or 0.7kg- 8.5g root (1.6lbs - 0.3oz)	death due to severely impaired liver function but mild histological damage	
		17.8 mg/kg	thrice weekly for 3 weeks	1.2kg - 8g leaf (2.6lbs - 0.3oz) or 180g -2g root (6oz - 0.07 oz)	reduced liver function (liver histology not checked)	
			thrice weekly for 9 weeks	megalocytosis		
		8.9 mg/kg	thrice weekly for 3 weeks	0.6 kg - 4g leaf) (1.3 lb - 0.1 oz) or 89g - 1g root (3oz - 0.04oz)	reduced liver function (liver histology not checked)	
Rats young adults	Total Symphytum PA (oral)	200mg/kg	Single dose	13kg - 91 g leaf (29lbs -3 oz) or 2kg - 24g root (4.4 lbs - 0.9 oz)	All rats showed evidence of liver damage that was dose dependent.	[76]
		100mg/kg	thrice weekly for 3 weeks	6.7kg - 45g leaf (15 lbs - 1.6 oz) or 1kg - 12 g root (2.2 lbs - 0.4oz)		
		50 mg/kg	thrice weekly for 3 weeks	3.3kg - 23g leaf (7.3 lbs - 0.8oz) or 0.5kg - 6g root (1 lb - 0.2 oz)		
		50mg/kg	once a week for 6 weeks	3.3kg - 23 g leaf (7.3 lbs - 0.8oz) or 0.5kg -6g root (1 lb -0.2 oz)		[101]

^a Ranges calculated based on data from table 3: leaf contains between 15 and 2200? g total alkaloids./g and root contains between 100 and 83\230? g total alkaloids/g.

^b Given 5% of comfrey PA are symphytine ^[65]

^c Alternately if all alkaloids have equivalent toxicity to symphytine.

^d Assuming echimidine is one half to a third of the concentration of symphytine ^[82].

^e Assuming rat eats 10g/day and weighs 100g

^f Proliferation of the intrahepatic bile duct, megalocytosis, hyperplastic nodule or liver cirrhosis was encountered frequently, even in rats without tumors.