

The uses of animal models in the evaluation of functional foods

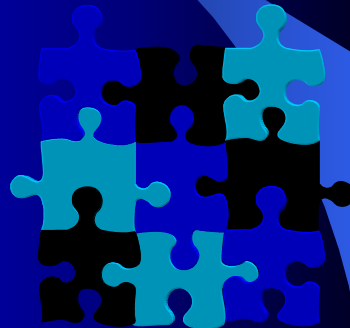


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November 30, 2006

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Content

- Assessments for health claims on foods or food ingredients
- Animal models
 - species
 - models
 - treatments
- Future application



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Health claims on foods or food ingredients

- 安全性評估
 - 基因毒性試驗
 - 餵食毒性實驗
 - 致畸試驗
 - 致癌試驗
 - 繁殖試驗
- 功能性評估
 - 公告：9項+2項

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Functional Evaluations

- 調節血脂功能
- 腸胃功能改善
 - 促進消化吸收
 - 改善腸內細菌菌相
 - 幫助(改善)胃腸蠕動
 - 助於胃黏膜保護作用
- 改善骨質疏鬆
- 牙齒保健功能

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Functional Evaluations

- 免疫調節功能
- 調節血糖功能
- 護肝功能(化學性肝損傷)
- 抗疲勞功能
- 延緩衰老功能
- 促進鐵吸收功能(96.01.01生效)
- 輔助調節血壓功能(96.01.01生效)
- 不易形成體脂肪功能(草案)

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Selection of Animal Models

- significance
- validity
- homologous
- a good knowledge of comparative anatomy and physiology



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Classification of disease Models

- **induced (experimental) disease models**
- **spontaneous (genetic) disease models**
- **transgenic disease models**
- **negative disease models**
- **orphan disease models**

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General Considerations

- **appropriateness as an analog**
- **transferability of information**
- **genetic uniformity of organisms**
- **background knowledge of biological properties**
- **cost and availability**
- **generalizability of the results**
- **ease of and adaptability to experimental manipulation**

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General Considerations

- ecological consequences
- ethical implications
- housing availability
- size of animal
- numbers needed
- life span
- sex
- amount of data needed
- age of animal
- progeny needed

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General Requirements

- taking a plurispecies approach
toxicology screening: rodents & non-rodents
- metabolic patterns and speed and body size must match between species
- confounding variables of metabolism must be controlled
- experimental design and the life situation of the target species must correspond

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Animal Models-Mice

- Balb/c mice: 近交系，免疫調節、幽門螺旋感染潰瘍
- B6 (C57BL/6J) mice: 近交系，免疫調節
- ICR mice: 遠交系，護肝
- Hamsters: 調整血脂



Balb/c mouse



B6 mouse



ICR mouse



hamster

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Animal Models-Rats

- Wistar rats: 遠交系，抗疲勞、促鐵吸收、護肝
- Sprague Dawley (SD) rats: 胃腸功能改善、護肝



SD rat



Wistar rat

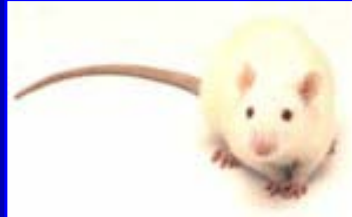
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Animal Models

- Spontaneously hypertensive rats (SHR):
近交系Wistar Kyoto rats , 調整血壓
- F344 rats:近交系 , 癌症研究



SHR rat



F344 rat

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Animal Models-Gene Mutation

- ob/ob mice: C57BL/6J mice, ob gene mutation, obese/diabetic
adiposity → obesity
insulin resistance → hyperinsulinemia
Hyperglycemia → diabetes
- db/db mice: leptin receptor gene mutation, obese/diabetic
hyperinsulinemia
hyperglycemia
hyperleptinemia
obesity

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Animal Models-Type 1 DM

- **Non-obese diabetic (NOD) mouse: ICR mouse**
- **liver glucokinase knockout mouse**
- **BB rat: Wistar rat**
- **Streptozotocin- or alloxane-induced model: rabbits, cats, dogs, rodents, primates**
- **Pancreatectomy model: dogs**

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Animal Models-Type 2 DM, Obesity

- **Zucker-Diabetic-Fatty (ZDF) rat**
- **Otsuka-Long-Evans-Tokushima -Fatty (OLETF) rat**
- **KK mouse**
- **db/db mouse**
- **ob/ob mouse**
- **New Zealand obese (NZO) mouse**
- **Tsumura-Suzuki obese diabetic (TSOD) mouse**
- **TallyHo (TH) mouse**
- **Goto-Kakizaki rat: Wistar rat**

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Animal Models-Cancer

- Transgenic mice
- C57BL/6J-Trp53^{tm1Tyj}
p53 gene mutation
lymphoma, osteosarcoma
- TgN(WapHRAS)69LIn Y^{SJL}
ras gene mutation
lung cancer, breast cancer

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Animal Models-Immune Deficiency

- Balb/c-nu mice: 近交系，無胸腺，缺乏T細胞，免疫腫瘤疾病研究
- Severe combined immune deficiency (SCID) mice: 缺乏T與B細胞，免疫腫瘤疾病研究

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Animal Models-CVD

- Vascular disease-hypertension
- SHR
- SHRSP (stroke-prone SHR)

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Animal Models-CVD

- Cardiovascular disease
- C57BL/6J-Apoe^{tm1Unc}: Apo E (ligand for LDL receptors) defect
atherosclerosis
hypercholestrolemia
Alzheimer's disease
neurodegeneration
- C57BL/6J-TgN (APOA1)^{1Rub}: Apo A1 (cofactor for lecithin cholesterol acyltransferase-LCAT) defect
hypercholestrolemia

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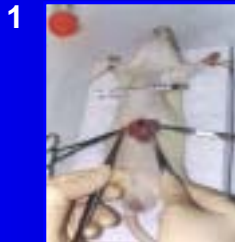
Animal Models-Liver Injury

- chronic bile duct ligation (CBDL) *Green et al. 1995*
- portal vein ligation (PVL) *Huang et al. 1997*
- chemical toxicity
 - **carbon tetrachloride** (CCl_4) *Cameron et al. 1936*
 - D-galactosamine *Jezequel et al. 1987*
 - Dimethylnitrosamine (DMN) *Burck et al. 1988*

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Animal Models-Peptic Ulcer

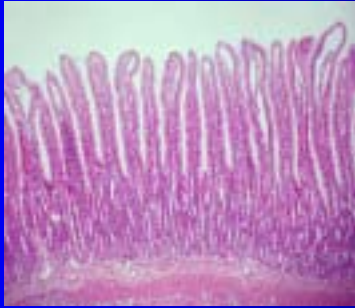
- acetic acid-induced ulcer
30%~50% acetic acid for 10~15 s



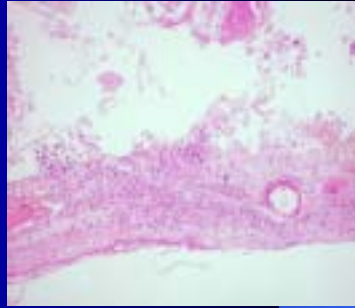
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Duodenal Ulcer

A



B



A: sham operation rats ($\times 200$)

B: duodenal ulcer rats ($\times 100$)

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Treatment-Type

- consider feasibility, taste
- solid: chow diet, powder, tablet, capsule
- semi-liquid
- liquid
 - water-soluble
 - water-insoluble

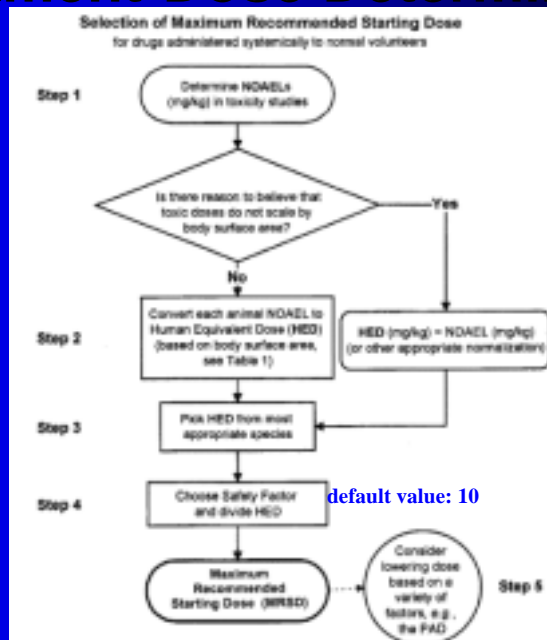
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Treatment-Dose

- within or beyond physiological level
- diet component or supplement
- toxicity
- units
 - % feed weight
 - % energy
 - dosage (mg)/kg body weight
- conversion dose
- pair-fed (if applicable)
- adjust dose of other diet components
 - isocaloric diet

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Treatment-Dose Determination



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Treatment-Dose

- based on body weight

$$\text{Human equivalent dose (HED)} = \text{Animal dose (mg/kg)} \times [\text{animal weight (kg)} \div \text{human weight (kg)}]^{0.33}$$

- based on body surface

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Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area				
Species	To convert animal dose in mg/kg to dose in mg/m ² , multiply by km below:		To convert animal dose in mg/kg to HED in mg/kg, either:	
			Divide animal dose by:	Multiply Animal dose by:
Human	37		---	---
Child (20 kg)	25		---	---
Mouse	3		12.3	0.08
Hamster	5		7.4	0.13
Rat	6		6.2	0.16
Ferret	7		5.3	0.19
Guinea pig	8		4.6	0.22
Rabbit	12		3.1	0.32
Dog	20		1.8	0.54
Primates:				
Monkeys	12		3.1	0.32
Marmoset	6		6.2	0.16
Squirrel monkey	7		5.3	0.19
Baboon	20		1.8	0.54
Micro-pig	27		1.4	0.73
Mini-pig	35		1.1	0.95

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Dose Conversion Between Species

Converted factor (A→B)		A						
		Mouse 0.02 kg	Rat 0.2 kg	Guinea pig 0.4 kg	Rabbit 1.5 kg	Cat 2 kg	Dog 12 kg	Adult 60 kg
B	Mouse 0.02 kg	1.0	1.4	1.6	2.7	3.2	4.8	9.01
	Rat 0.2 kg	0.7	1.0	1.14	1.88	2.3	3.6	6.25
	Guinea pig 0.4 kg	0.61	0.87	1.0	1.65	2.05	3.0	5.55
	Rabbit 1.5 kg	0.37	0.52	0.6	1.0	1.23	1.76	2.3
	Cat 2 kg	0.3	0.42	0.48	1.81	1.0	1.44	2.7
	Dog 12 kg	0.21	0.28	0.34	0.56	0.68	1.0	1.88
	Adult 60 kg	0.11	0.16	0.18	0.304	0.371	0.531	1.0

苗明三 1997 29

Treatment-Dose Calculation

Rat (0.15 kg): 50 mg/kg No observed adverse effect level (NOAEL)

- based on body weight

$$\text{HED} = 50 \times (0.15 \div 60)^{0.33} = 6.9 \approx 7.0 \text{ (mg/kg)}$$

- based on body surface

$$\text{HED} = 50 \times 0.16 = 8 \text{ (mg/kg)}$$

Treatment-Route

- oral
 - feed, drink
- tube feeding
 - gastric gavage
 - enteral feeding
 - total parental feeding
- Injection
 - intravenous (iv)
 - intraperitoneal (ip)
- skin
 - pad
 - cream/ointment/paste

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Treatment-time

- time
 - before meal
 - with meal
 - after meal
- frequency
 - single dose
 - multiple doses

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Future Application

- food or drug ?
- prevention of therapy ?

