

實驗動物疼痛焦慮之 辨識與評估

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■動物保護法 第十五條：

使用動物進行科學應用，應以使動物產生最少痛苦及傷害之方式為之

■動物保護法 第十七條：

科學應用後，應立即檢視實驗動物之狀況，如其已失去部分肢體器官或仍持續承受痛苦，而足以影響其生存品質者，應立即以產生最少痛苦之方式宰殺之

實驗動物經科學應用後，除有科學應用上之需要，應待其完全恢復生理功能後，使得再進行科學應用

在進行動物試驗時，應盡一切可能避免或減輕因手術等相關操作在動物體所引發之疼痛或痛苦

3R's

- **Replacement-** Use of nonanimal system or less-sentient animal species to partially or fully replace animals.
- **Reduction-** Reduction in the number of animals utilized to the minimum required to obtain scientifically valid data.
- **Refinement-** Use of a method that lessens or eliminates pain and/or distress and therefore enhances animal well-being.

The *Guide*

- Justification of the species and number of animals requested.
- Availability or appropriateness of the use of less-invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation.
- Appropriate sedation, analgesia, and anesthesia.
- Unnecessary duplication of experiments.

Stress

- An effect produced by external (i.e., physical or environmental) events or internal (i.e., physiologic or psychologic) factors, referred to as **stressors**, which induce an alteration in an animal's biologic equilibrium.
- Responses to stressors often involve changes in physiologic function (biochemical, endocrinologic, or autonomic), psychologic state, and behavior.
- An animal's response can vary according to its age, sex, experience, genetic profile, and present physiologic and psychologic state.
- **Stress might not be harmful to an animal**; it might evoke responses that neither improve nor threaten an animal's well-being.

Distress

- An aversive state in which an animal is unable to adapt completely to stressors and the resulting stress and shows **maladaptive behaviors**.
- **Stressor**- fear, pain, malaise, anxiety, frustration, depression, boredom...
- **Maladaptive behaviors**- abnormal feeding, aggression, hypertension, immunosuppression.

Pain

- Pain is an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in such terms.
- Pain is **stressor**.
- Can lead to distress and maladaptive behaviors.
- Behaviors responses- simple withdrawal reflexes, vocalization, and learned responses ranging from guarding an injured limb to attempting to escape, avoid, or terminate a painful stimulus.
- Physiologic responses- changes in blood pressure and heart rate.
- “Fundamental to the relief of pain in animals is the ability to recognize its clinical signs in specific species” (*The Guide*. p.64).

Potential Stressors

That Cause Physiologic Stress		That Cause Psychologic Stress	That Cause Environmental Stress
Injury	} pain	Fear	Restraint
Surgery		Anxiety	Noise
Disease		Boredom	Odors
Starvation		Loneliness	Habitat
Dehydration		Separation	Ecology
			People
			Other species
			Chemicals
			Pheromones

Indicators of Pain in Laboratory Animals

Species	General Behavior	Appearance	Other
Rodents	Decreased activity; excessive licking and scratching; self-mutilation; may be unusually aggressive; abnormal locomotion (stumbling, falling); writhing; does not make nest; hiding	Piloerection; rough/stained haircoat; abnormal stance or arched back; porphyrin staining (rats)	Rapid, shallow respiration; decreased food/water consumption; tremors
Rabbit	Head pressing; teeth grinding; may become more aggressive; increased vocalizations; excessive licking and scratching; reluctant to locomote	Excessive salivation; hunched posture	Rapid, shallow respiration; decreased food/water consumption
Dog	Excessive licking; increased aggression; increased vocalizations, inclusive of whimpering, howling, and growling; excessive licking and scratching; self-mutilation	Stiff body movements; reluctant to move; trembling; guarding	Decreased food/water consumption; increased respiration rate/panting
Cat	Hiding; increased vocalizations, inclusive of growling and hissing; excessive licking; increased aggression	Stiff body movements; reluctant to move; haircoat appear rough, ungroomed; hunched posture; irritable tail twitching; flattened ears	Decreased food/water consumption
Non-human Primate	Increased aggression or depression; self-mutilation; often a dramatic change in routine behavior (e.g., locomotion is decreased); rubbing or picking at painful location	Stiff body movements; reluctant to move; huddled body posture	Decreased food/water consumption

Potential Causes of Stress in Laboratory Animals

Husbandry Practices

- Inappropriate or variable temperature, humidity, ventilation, or illumination
- Inappropriate cage or enclosure size
- Noise
- Too infrequent change in bedding or removal of waste
- Stale food or dirty water
- Denial of positive social stimulation
- Maternal deprivation
- Social intimidation or abuse by companions
- Unprofessional behaviors or practices

Experimental Design

- Food and water deprivation
- Inadequate caging
- Poor or inappropriate technique
- Failure to adapt or handle animals
- Restraint
- Social deprivation
- Frequent changes in procedures or personnel

Pain and Distress

Column C

- Description: Testing, teaching, or experiments involving no pain, distress, or use of pain-relieving medications. Again, recognize that pain or distress must be more than slight or momentary to be, by definition, a painful procedure.
- Example: Collection of a blood sample from a peripheral vein not resulting in pain or distress. The animal remains calm throughout.

Column D

- Description: Testing, teaching, or experiments involving pain or distress for which appropriate analgesic, anesthetic, or tranquilizing drugs are used.
- Examples: (1) Use of an anesthetic agent to prevent pain or distress associated with intercardiac blood collection or perhaps any number of other types of procedures. (2) Use of a therapeutic agent to remedy an intentionally induced disease process. It would be a bit of a leap from where we are now, since current regulations recognize only anesthetics, analgesics, and tranquilizers or other pain-relieving medications as a means to appropriately classify procedures in Column D.

Column E

- Description: Teaching, testing, or experiments involving pain or distress for which the use of appropriate anesthetic, analgesics, or tranquilizing drugs would have adversely affected the procedure 's results or the interpretation.
- Examples: (1) Collection of an intercardiac blood sample without the use of pain-relieving medications. (2) Presence of an experimentally induced disease process that causes pain or distress that is not relieved by the use of pain-relieving medications.

Assessment of Pain

Behavioral

Grooming

Appetite

Activity

Aggression

Facial expression

Vocalization

Appearance

Posture

Response to
handling

Physiologic

Temperature

Pulse

Respiration

Weight loss

Blood-cell count

Blood-cell structure

Cardiac output

Blood flow

Biochemical

Corticosteroids

Catecholamines

Thyroxin

Prolactin

-Endorphin

ACTH

Glucagon

Insulin

Vasopressin

Substance P

Assessment of Distress

- **General schemes-** change in metabolic function, or evidence of maladaptive behavior
- **Physiologic and behavioral changes-** motor tension (shakiness and jumpiness), hyperactivity of the sympathetic nervous system (sweating, increased respiration and heart rate, and frequent urination), hyperattentiveness (increased vigilance and scanning)
- **Animal behavior-** distinguish adaptive behaviors from maladaptive behaviors, such as self-mutilation, unresponsiveness to important signals, hyperactivity, excessive response to stimulation.

Alleviation of Pain and/or Distress

- Pharmacological Control :

Use of general anesthesia/ Local anesthesia

Analgesia

- Nonpharmacological Control:

Nesting materials,

Environmental change

Experimental Design

- Euthanasia

- Veterinarian

Animal well-being

- Animal observations
- Animal Behavior

Humane Endpoints

- Endpoints are established for both experimental and humane reasons.

- IACUCs, PIs, veterinarians

General categories of endpoints-

- biologic markers:
 - development of paralysis in models of neural tumors
- markers of therapeutic failure:
 - persistent signs of tumor growth despite drug intervention
- markers of disability:
 - inability to stand in models of bacterial endotoxemia
- markers of disease exacerbation:
 - increased seizure frequency
- general markers of clinical deterioration:
 - substantial changes in body weight, alertness, respiration, and B.T.

表一 疼痛程度評估表（大鼠）

	評估項目	輕微疼痛	中度疼痛	嚴重疼痛
體重 (不包含暫時性體重減輕)	*體重 *食物/飲水消耗	*體重減少原體重的10%以下 *72小時內僅攝食正常量的40-75%	*體重減少原體重的10-25% *72小時內攝食低於正常量的40%以下	*體重減少原體重的25%以上 *7天內攝食低於正常量的40%，或食慾不振超過72小時
外觀	*身體姿勢 *毛髮豎起情形	*短暫的拱背，特別是在投藥後 *部分毛髮豎起	*間歇性拱背 *明顯皮毛粗糙	*持續性的拱背 *明顯皮毛粗糙，並伴隨其他症狀如拱背、遲鈍反應及行為
臨床症狀	*呼吸 *流涎 *震顫 *痙攣 *沉鬱、臥倒	*正常 *短暫的 *短暫的 *無 *無	*間歇性的呼吸異常 *間歇性的弄濕下顎附近的皮毛 *間歇性的 *間歇性的（每次10分鐘以下） *短暫的（1小時以下）	*持續性的呼吸困難 *持續性弄濕下顎附近的皮毛 *持續性的 *持續性的（若每次超過10分鐘以上，則建議安樂死） *持續超過1小時以上（若每次超過3小時以上，則建議安樂死）
無刺激時一般行為	*社會化行為	*與群體有對等的互動	*與群體的互動較少	*沒有任何的互動
對刺激的反應	*受刺激時行為反應	*變化不大	*受刺激時會有較少的反應（如：被人捉拿）	*對刺激或外部行為無任何的反應

表二 疼痛程度評估表（小鼠）

	評估項目	輕微程度	中等程度	嚴重程度
體重	*體重	*體重減少原體重的10%以下	*體重減少原體重的10-25%	*體重減少原體重的25%以上
外觀	*身體姿勢 *毛髮豎起情形	*短暫的拱背，特別是在投藥後 *部分毛髮豎起	*間歇性拱背 *明顯皮毛粗糙	*持續性拱背 *明顯皮毛粗糙，並伴隨其他症狀如拱背、遲鈍反應及行為
臨床症狀	*呼吸 *流涎 *震顫 *痙攣 *沉鬱. 臥倒	*正常 *短暫的 *短暫的 *無 *無	*間歇性的呼吸異常 *間歇性的弄濕下顎附近的皮毛 *間歇性 *間歇性（每次10分鐘以下） *短暫的（1小時以下）	*持續性呼吸困難 *持續性的弄濕下顎附近的皮毛 *持續性 *持續性（若每次超過10分鐘以上，則建議安樂死） *持續1小時以上（若每次超過3小時以上，則建議安樂死）
無刺激時一般行為	*社會化行為	*與群體有對等的互動	*與群體的互動較少	*沒有任何的互動行為
對刺激的反應	*受刺激時行為反應	*變化不大	*受刺激時亦壓抑行為反應(如：被人捉拿時)	*對刺激或外部行為無任何反應

表三 疼痛程度評估表（天竺鼠）

	評估項目	輕微疼痛	中度疼痛	嚴重疼痛
體重	*體重 *食物/飲水 消耗	*體重減少原體重的10%以下 *72小時內攝食正常量的40-75%	*體重減少原體重的10-25% *72小時內攝食低於正常量的40%以下	*體重減少原體重的25%以上 *7天內攝食低於正常量的40%以下，或食慾不振超過72小時
外觀	*皮毛狀況 *身體姿勢	*局部掉毛 *短暫的拱背，特別是在投藥後	*明顯皮毛粗糙，脫毛 *間歇性的拱背	*明顯皮毛粗糙，並伴隨其他症狀如拱背、遲鈍反應及行為 *持續性的拱背
臨床症狀	*呼吸 *流涎 *震顫 *痙攣 *沉鬱. 臥倒	*正常 *短暫的 *短暫的（特別是在處理動物的時候） *無 *無	*間歇性的呼吸異常 *間歇性的弄濕下顎附近的皮毛 *間歇性 *間歇性（每次10分鐘以下） *短暫的（1小時以下）	*持續性的呼吸困難 *持續性的弄濕下顎附近的皮毛 *持續性的 *持續性的（若每次痙攣超過10分鐘以上，則建議安樂死） *持續1小時以上（若每次超過3小時，則建議安樂死）
無刺激時一般行為	*社會化行為 *發聲狀況	*與群體有對等的互動 *發出正常音頻的叫聲	*與群體的互動較少 *受刺激的時候發出間歇性的、悲傷的、沉鬱的叫聲	*沒有任何的互動行為 *發出悲傷的、沉鬱的叫聲，亦可能完全不叫
對刺激的反應	*受刺激時行為反應	*壓抑，但受刺激時還有正常行為反應	*受刺激時亦壓抑行為反應	*對刺激或外部行為無任何反應

表四 疼痛程度評估表（倉鼠）

	評估項目	輕微疼痛	中度疼痛	嚴重疼痛
體重	*體重 *食物/飲水消耗	*體重減少原體重的10%以下 *72小時內攝食正常量的40-75%	*體重減少原體重的10-25% *72小時內攝食低於正常量的40%以下	*體重減少原體重的25%以上 *7天內攝食低於正常量40%或食慾不振超過72小時
外觀	*皮毛狀況 *身體姿勢	*正常 *短暫的拱背，特別是在投藥後	*皮毛無光澤，較少整理皮毛 *間歇性拱背	*嚴重皮毛粗糙，完全不整理毛髮，並伴隨其他症狀如拱背、遲鈍反應及行為 *持續性拱背
臨床症狀	*震顫 *痙攣 *沉鬱、臥倒	*短暫的 *無 *無	*間歇性 *間歇性（每次10分鐘以下） *短暫的（1小時以下）	*持續性 *持續性（若每次超過10分鐘以上，則建議安樂死） *持續超過1小時（若每次超過3小時，則建議安樂死）
無刺激時一般行為	*發聲狀況	*發出正常音頻的聲音	*間歇性的發出悲傷的、沉鬱的叫聲	*發出悲傷的、沉鬱的叫聲，亦可能完全不叫
對刺激的反應	*受刺激時行為反應	*變化不大	*受刺激時有較小且溫和的反應	*對刺激或外部行為無任何反應

表五 疼痛程度評估表（兔子）

	評估項目	輕微程度	中等程度	嚴重程度
體重	*體重 *食物/飲水消耗	*體重減少原體重的10%以下 *72小時內攝食正常量的40-75%	*體重減少原體重的10-25% *72小時內攝食低於正常量的40%以下，或食慾不振超過48小時	*體重減少原體重的25%以上 *7天內攝食低於正常量的40%以下，或食慾不振超過72小時
外觀	*皮毛狀況 *身體姿勢	*正常 *短暫的拱背，特別是在投藥後	*皮毛無光澤，較少整理毛髮 *間歇性的拱背	*明顯皮毛粗糙，完全不整理毛髮，並伴隨其他症狀如拱背、遲鈍反應及行為 *持續性的拱背
臨床症狀	*呼吸 *流涎 *震顫 *痙攣 *沉鬱、臥倒	*正常 *短暫的 *短暫的 *無 *無	*間歇性的呼吸異常 *間歇性的弄濕下顎附近的皮毛 *間歇性 *間歇性（每次10分鐘以下） *短暫的（30分鐘以下）	*持續性呼吸困難 *持續性的弄濕下顎附近的皮毛 *持續性 *持續性（若每次超過10分鐘以上，則建議安樂死） *持續30分鐘以上（若每次超過1小時以上，則建議安樂死）
無刺激時一般行為	*社會化行為 *發聲狀況	*與群體有對等的互動	*與群體的互動較少	*沒有任何的互動行為 *發出類似悲傷痛苦的叫聲
對刺激的反應	*受刺激時行為反應	*正常反應	*受刺激時亦壓抑行為反應	*對刺激或外部行為無任何反應

表六 疼痛程度評估表（米格魯犬）

	評估項目	輕微疼痛	中度疼痛	嚴重疼痛
體重	*體重 *食物/飲水消耗	*7天間減少原體重的10%以下 *72小時內僅攝食正常量的40-75%	*7天間減少原體重的10-25% *72小時內攝食低於正常量的40%以下	*7天間減少原體重的25%以上 *7天間攝食低於正常量的40%以下或食慾不振超過72小時
外觀	*皮毛狀況 *身體姿勢	*正常 *正常	*皮毛無光澤，較少整理皮毛 *間歇性有hang dog姿勢	*皮毛狀況非常差，不整理皮毛，並伴隨有其他如'hang dog'症狀、遲鈍反應及行為 *持續性有'hang dog'姿勢
臨床症狀	*呼吸 *震顫 *痙攣 *沉鬱. 臥倒	*正常 *短暫的 *無 *無	*間歇性呼吸異常 *間歇性 *間歇性（每次10分鐘以下） *短暫的（1小時以下）	*持續性呼吸困難 *持續性 *持續性（若每次痙攣超過10分鐘以上，則建議安樂死） *持續1小時以上（若持續超過2小時以上，則建議安樂死）
無刺激時一般行為	*社會化行為	*與群體有對等的互動	*與群體的互動較少	*沒有任何的互動行為
對刺激的反應	*受刺激時行為反應	*受刺激時有溫和且正常反應	*受刺激時有較少的反應	*對刺激或外來行為無任何反應

Euthanasia

- The Report of the AVMA Panel on Euthanasia (AVMA, 2001)
- 農委會 <http://www.coa.gov.tw>

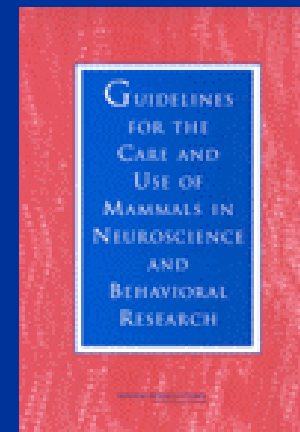
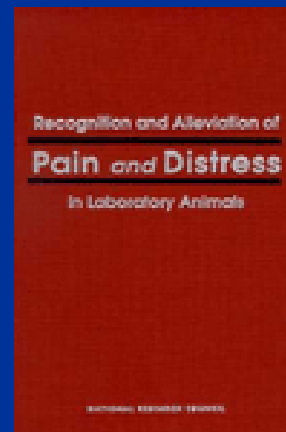
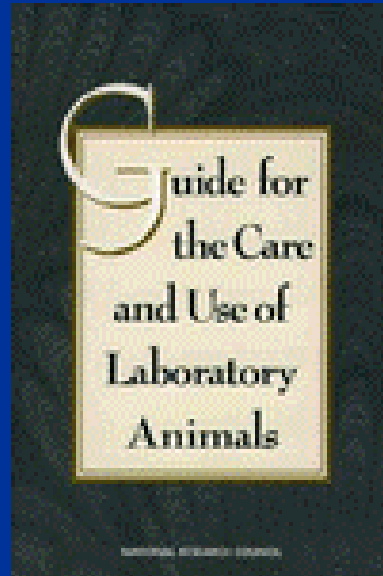
常用實驗動物建議安樂死方法

安樂死法	小於125 g 齧齒動物	125 g~ 1 kg 齧齒動物/兔	1 kg~ 5 kg 齧齒動物/兔	狗	貓	非人類靈 長類	反芻動物. 馬.豬
二氧化碳	○	○	○	×	×	×	×
Barbiturate注射液, 靜脈 注射 (100 mg/kg)	○	○	○	○	○	○	○
Barbiturate注射液, 腹腔 注射(100 mg/kg)	○	○	○	×	○	×	○
先麻醉, 之後採血(放血) 致死	○	○	○	○	○	○	○
先麻醉, 之後靜脈注射 KCl (1-2 meq/kg)	○	○	○	○	○	○	○
先麻醉, 之後斷頭	○	○	△	×	×	×	×
先麻醉, 之後頸椎脫臼	○	○	×	×	×	×	×
動物清醒中直接斷頭	△	△	△	×	×	×	×
動物清醒中直接頸椎脫臼	△	×	×	×	×	×	×
電擊	×	×	×	×	×	×	○

不建議使用之動物安樂死方法

方法	說明
空氣注射	此法導致動物痙攣、角弓反張和哀叫
打爛頭部	大多數動物皆不被接受
燒死	化學式或加熱燒死大多數動物皆不被接受
Chloral hydrate	狗、貓以及小型哺乳動物皆不得使用
氯仿Chloroform	具有肝毒性且可能有致癌性，有害於人
氰化物Cyanide	極有害於人
減壓法 Decompression	(1) 導致動物痛苦、垂死時間拉長 (2) 年幼動物耐缺氧狀態，因此需較長時間才能達呼吸停止 (3) 偶發動物甦醒的意外狀況 (4) 會導致動物出血、嘔吐、痙攣、排尿或排便等現象
溺斃	溺斃不是安樂死的方法，亦不人道
放血(採血)致死	大量失血導致動物焦慮及暴躁，放血(採血)致死僅適用於動物已鎮靜、暈倒或麻醉
福馬林	直接將動物浸泡於福馬林，是非常不人道的方法
家庭用產品或溶劑	丙酮類(如去光水), 四級元素(如 CCl_4)、瀉劑、丁香油、四級胺類產品、胃藥、等，皆不得使用
低溫致死	此法不適用於動物安樂死
神經肌肉阻斷劑	如尼古丁、硫酸鎂、KCl、以及其他curariform類南美箭毒製劑。此類藥物單獨使用時，皆造成動物呼吸抑制(暫停)後才失去意識，因此動物在無法動彈後亦遭受一段時間的痛苦和壓迫。
快速冷凍	此法不人道，如因實驗所需選用此法，動物需先深度麻醉
馬錢子素(番木鱉)Strychnine	此藥劑造成動物的劇烈痙攣和痛苦的肌肉抽續
打暈	此法不是動物安樂死法
Tricaine	methane sulfonate (TMS, MS 222)，食用動物勿用此藥劑

<http://www.nap.edu>



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