Defining Adverse, Non-adverse and Adaptive Responses in Safety/Risk Assessment

Robert R. Maronpot
Maronpot Consulting LLC
Raleigh, NC
maronpot@gmail.com

Honolulu, Hawaii July 15, 2019

Conflict of Interest Statement

The author declares no conflict of interest.

Outline of Presentation

- Definitions & Considerations
  - Adverse response
  - Non-adverse response
  - Adaptive response
  - Reversibility
  - Exacerbation of background lesions
- Communicating Adversity
- Paradigm Shift & Determining Adversity
- Practical Examples of Adverse and Adaptive Responses in Preclinical Studies

Adverse Response

- In very broad terms, an adverse finding may be considered to be a change (biochemical, functional, or structural) that may impair performance and generally has a detrimental effect on growth, development, or life span of a non-clinical toxicology model.
- More specifically, an adverse effect in a non-clinical toxicology study should be an effect that would be unacceptable if it occurred in a human clinical trial (FDA Guidance, 2002).

Dorato & Englehardt, Reg Tox & Pharmacol 42:265-274 (2005)

Adverse Response

- Defined in context of nonclinical toxicity study
- A change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub)population that likely results in:
  - impairment of functional capacity
  - impairment of the capacity to compensate for additional stress or
  - increase in susceptibility to other influences

Keller et al., Toxicol Sci 2012

No Observed Adverse Effect Level (NOAEL)

- Highest dose or exposure that does not cause a toxicologically relevant increase in frequency or severity of effects between exposed and control groups based on careful biological and statistical analysis.
- Minimum toxic or pharmacodynamic responses may occur at the NOAEL and may not endanger human health or be precursors to serious events with continued duration of exposure.

Dorato & Englehardt 2005

Factors to Consider in an Adversity Call

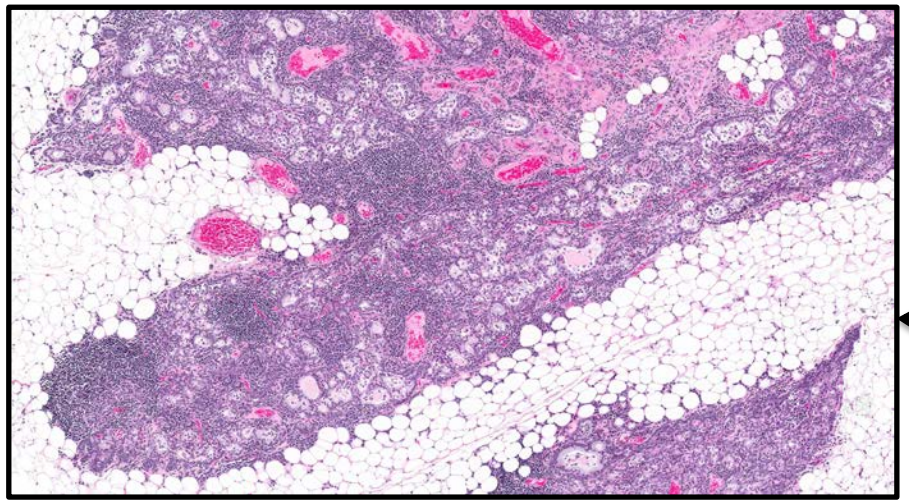
- Are there related pathological findings?
- Is there a known or biologically plausible underlying mechanism?
- What are the severity criteria?
- What is the background incidence (historical control)?

Are some findings non-adverse?

- Bile duct hyperplasia
- Lymphoid hyperplasia
- Microsomal enzyme induction
- Decreased serum ALT and AST
- Extramedullary hematopoiesis in liver

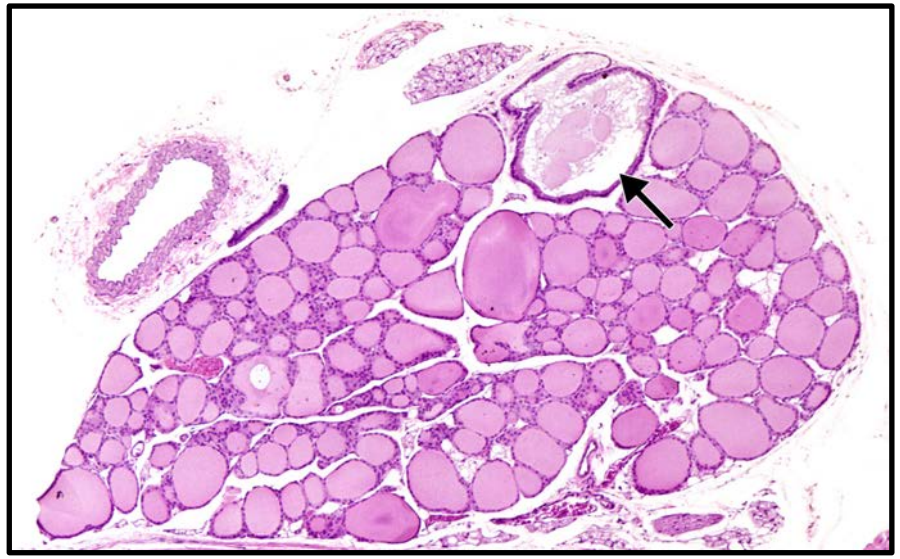
When findings such as these do not compromise normal tissue physiology, do not impair functional capacity, and do not increase susceptibility to other influences, then they may be considered non-adverse.

Some Examples of Non-Adverse Findings



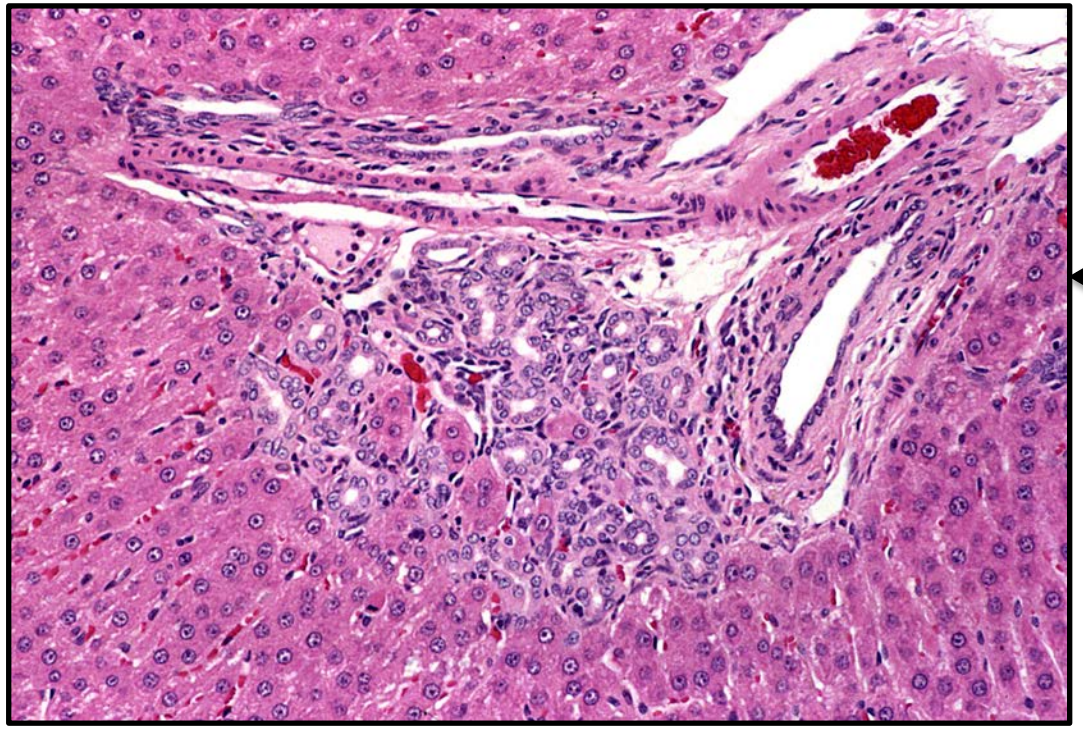
Thymic involution in a chronic rat study

However, this degree of thymic involution in a 90-day rat study would be an adverse response.



Congenital cyst in a rodent study

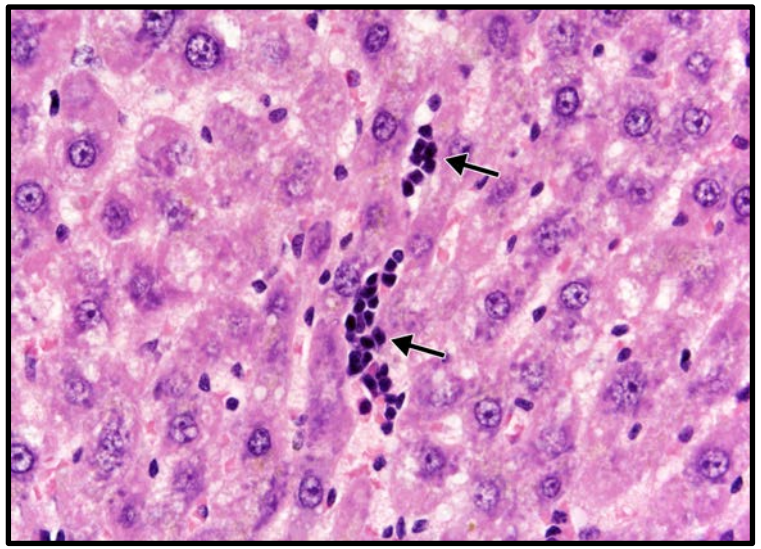
Another Example of a Non-Adverse Finding



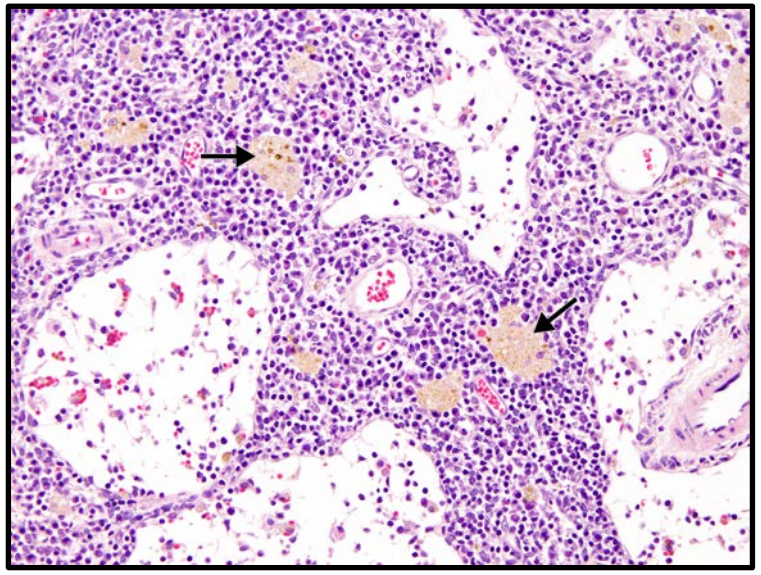
Bile duct hyperplasia in a chronic rat study

However, this degree of bile duct hyperplasia in a 90-day rat study would be an adverse response.

Other Examples of Non-Adverse Findings



Extramedullary hematopoiesis in the liver – a secondary response to bone marrow suppression



Pigment in a lymph node – a normal function in a draining lymph node

These secondary responses could be considered **adaptive** responses.

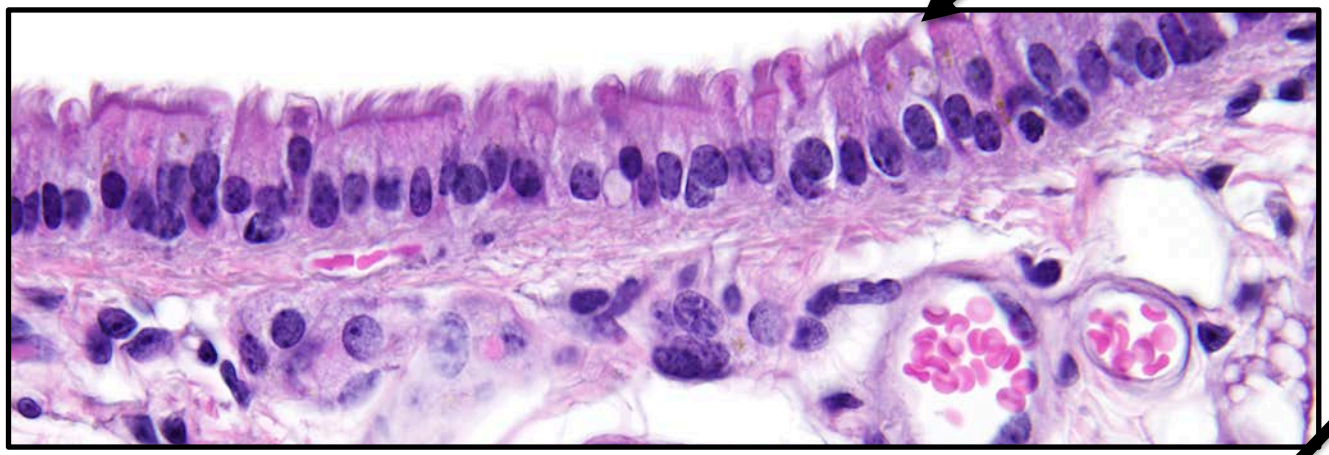
Adaptive Response

- In the context of a toxicology study, the process whereby a cell or organism responds to a xenobiotic so that the cell or organism will survive without impairment of function in the new environment that contains the xenobiotic.
  - An evolutionary strategy to survive in a new environment resulting from xenobiotic exposure
  - Basically there is a reset of homeostatic equilibrium for survival in that new environment; a new functional steady state in the new environment
- “Adaptive” and “adverse” are not mutually exclusive.
- Adaptive and some adverse responses may be reversible.

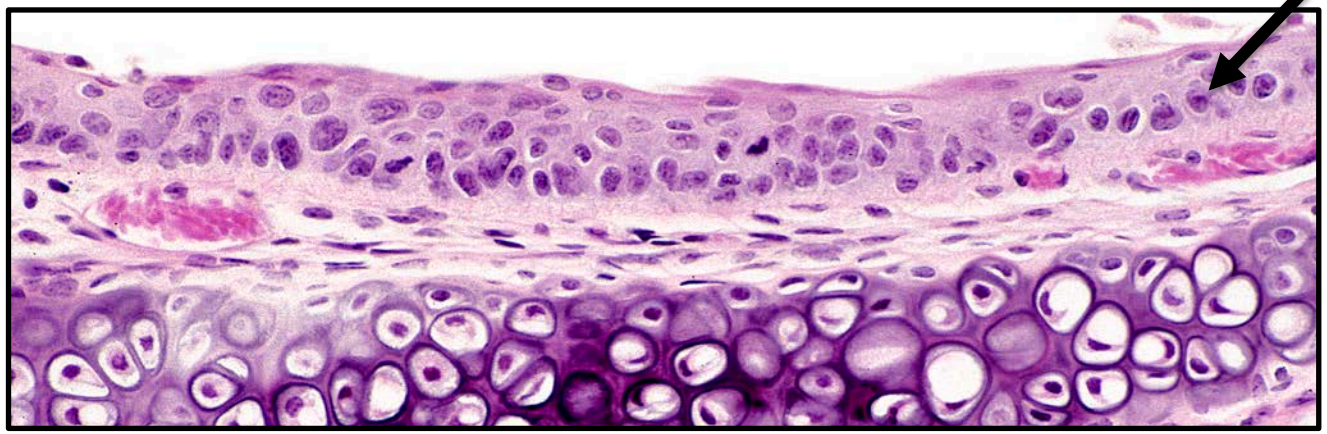
Adaptive Responses

- An adaptive change can sometimes be adverse

Normal ciliary epithelium in the trachea



Squamous metaplasia affects normal ciliary function in the trachea and is, therefore, an adaptive response that is adverse.



Even though it is potentially **reversible** after the cause is removed, it is still an adverse response.

Reversibility

- Response disappears after treatment is stopped
- Reversibility is typically determined using recovery groups in toxicity studies

What Determines if a Lesion is Reversible?

- Dependent upon the regenerative capacity of the tissue or organ
- Dependent of the type of lesion
  - Proliferative/non-proliferative
- Dependent on lesion severity
- Depends upon length of time after stopping treatment
  - Partial/complete reversibility

Reversibility

- An adverse lesion may or may not be reversible
- If an adverse lesion is reversible, then reversibility can be:

  A key component in weight-of-evidence in study interpretation

  May indicate a lower level of concern

Perry et al., 2013. Toxicologic Pathology 41: 1159-1169
Sewell et al., 2014. Regulatory Toxicology & Pharmacology 70: 414-429

Exacerbation

Exacerbation = an increase in the incidence and/or severity of an age-related and/or strain-specific common background lesion seen in control animals in a toxicity/carcinogenicity study

Can exacerbated background lesions be adverse?

Yes, if –

- the exacerbation is a biologically plausible primary effect of the test agent
- the exacerbation shows a clear dose-response
- the exacerbation exceeds historical control

Outline of Presentation

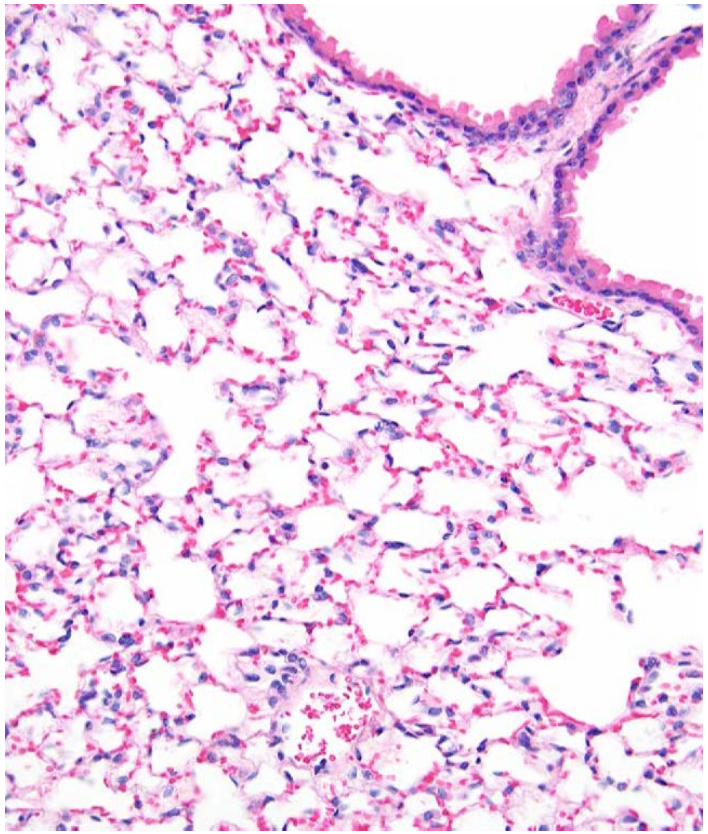
- Definitions
  - Adverse response
  - Adaptive response
  - Reversible response
  - Exacerbation of background lesions
- Communicating Adversity
- Paradigm Shift & Determining Adversity
- Practical Examples of Adverse and Adaptive Responses in Preclinical Studies

Communicating Adversity

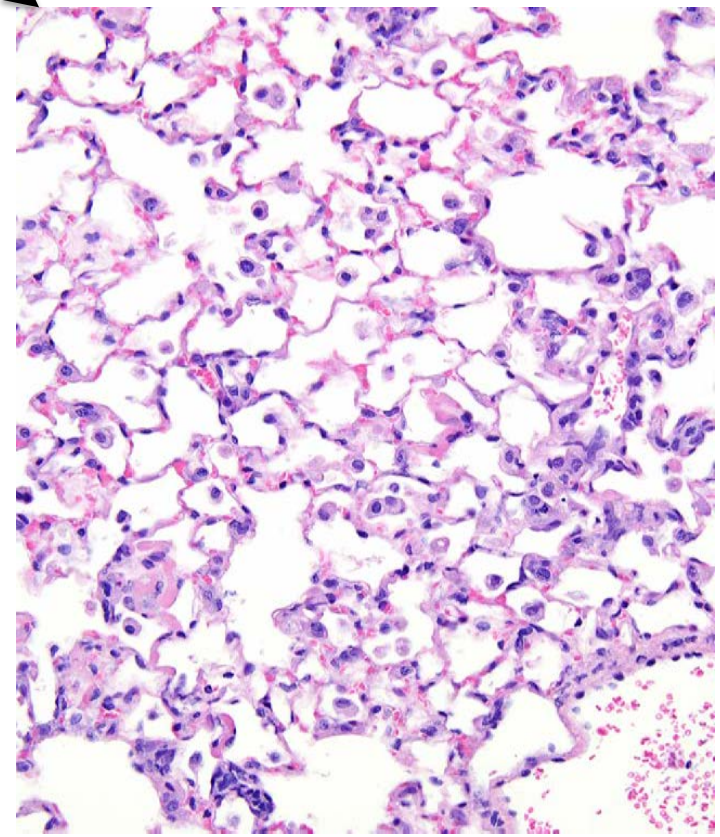
- Clearly characterize relevant changes & explain judgments regarding why a change is adverse or non-adverse
- Need detailed description of what is adverse for each health-related endpoint
  - Provide details on pathogenesis & mechanism
  - Explain morphological criteria for diagnoses and severity scoring
- Consider use of outside peer review & expert reports

An Example for the Toxicology Report and Regulatory Submission

Alveolar histiocytosis



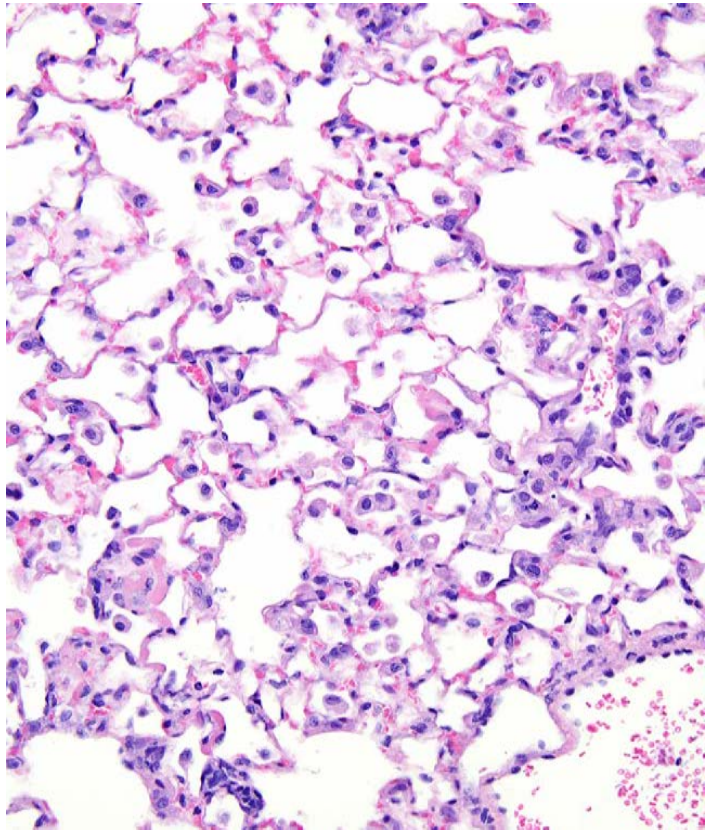
Control



Treated

For the Toxicology Report and Regulatory Submission

- In this example of alveolar histiocytosis:



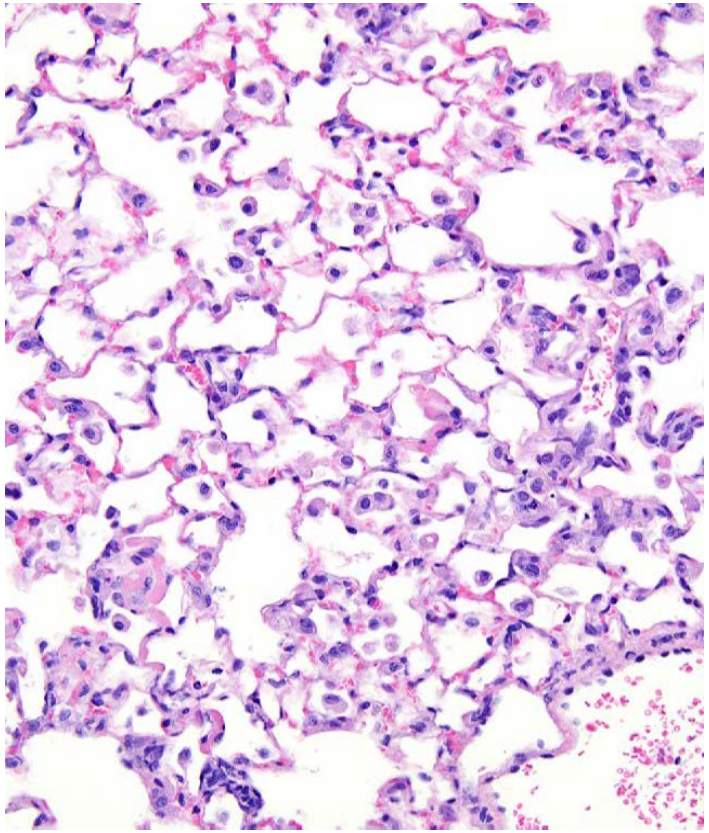
Treated

Sponsor considered the alveolar histiocytosis to be adaptive and non-adverse because…

- Inhalation study
- Serum enzymes were normal
- Minimal to mild increase in alveolar histiocytes
- No evidence of inflammation
- No epithelial hyperplasia

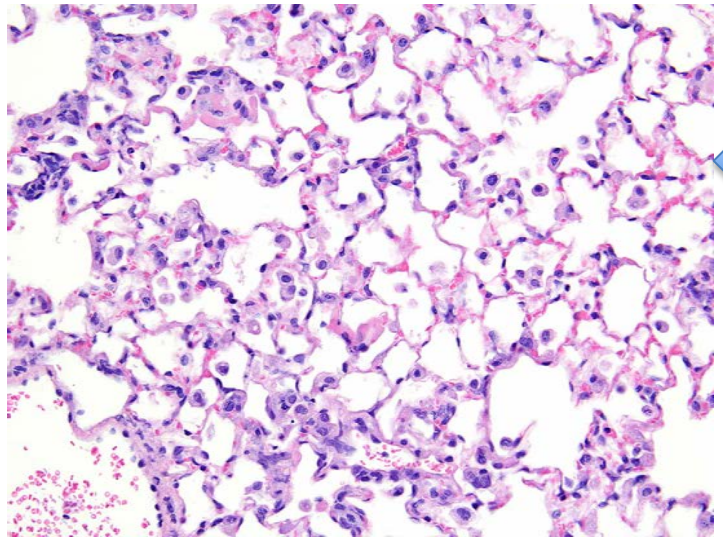
For the Toxicology Report and Regulatory Submission

- Citing relevant literature for histiocytosis example



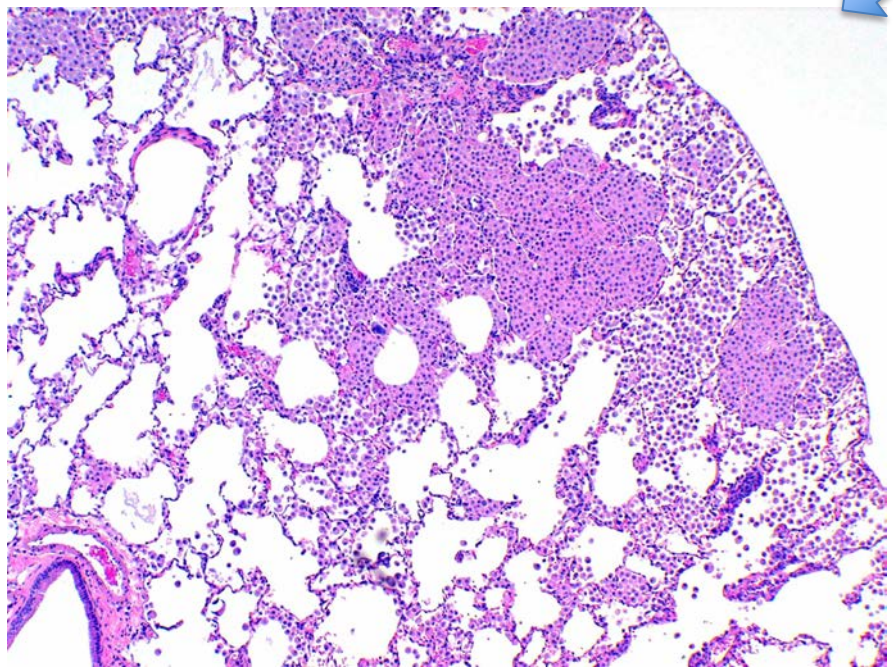
"An expert working group focused on distinguishing adaptive versus adverse responses in rodents and concluded that increases in alveolar macrophage number and/or size are not adverse if there are no other lung changes such as inflammation and/or hyperplastic epithelial responses."

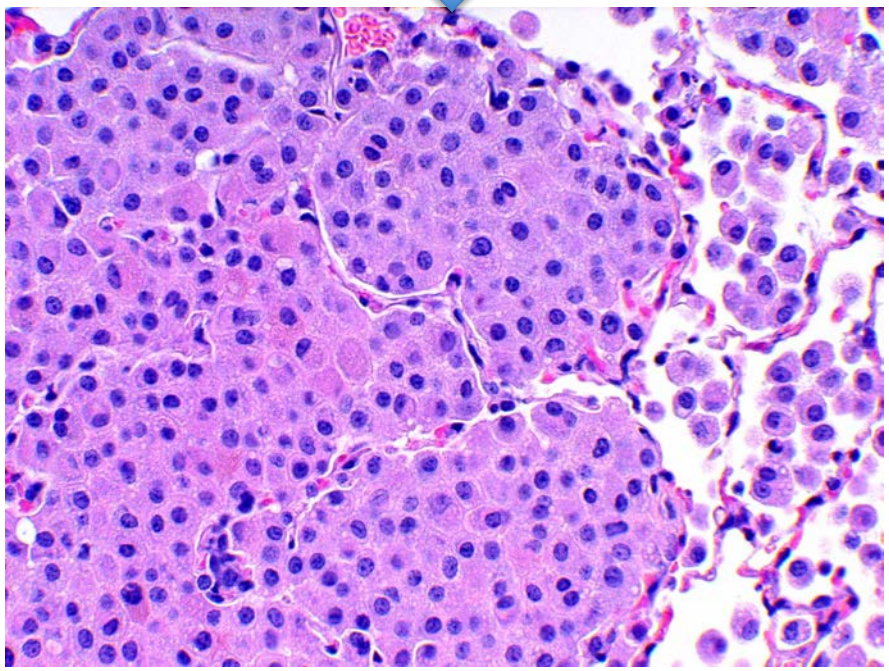
Nikula et al., 2014. Toxicologic Pathology 42:472-486.

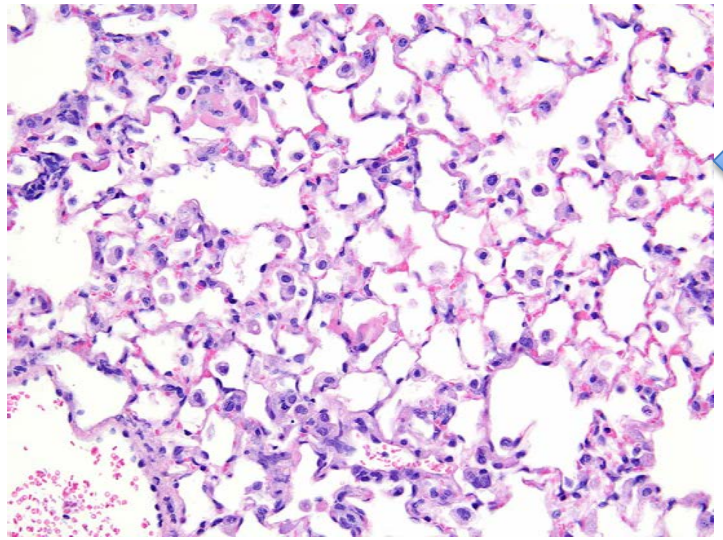


Minimal to mild alveolar histiocytosis reflects a macrophage response to changes in the local environment & represents a tissue adaptation to maintain normal lung function

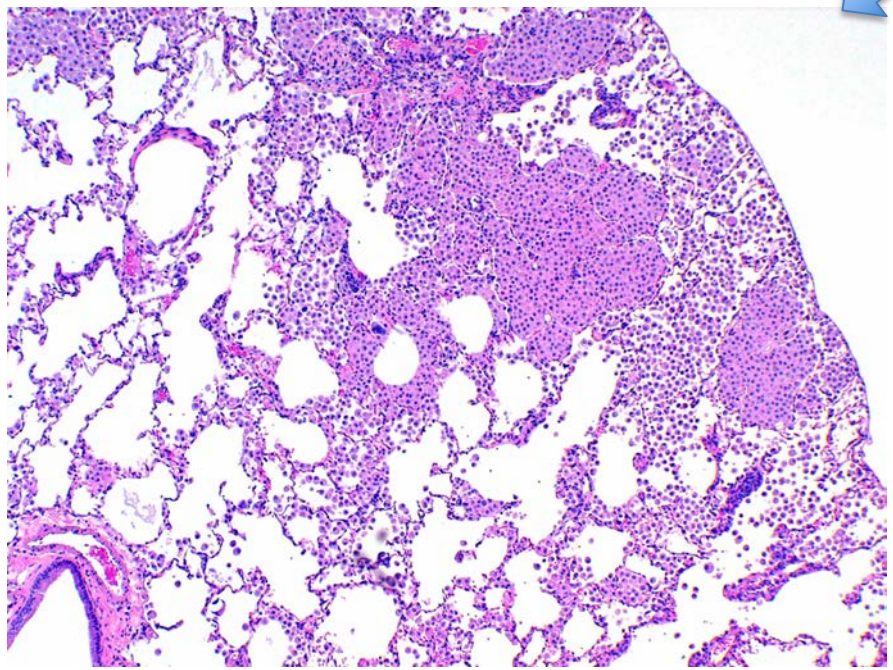
But severe alveolar histiocytosis as in this example represents an adverse response, even if it is reversible.

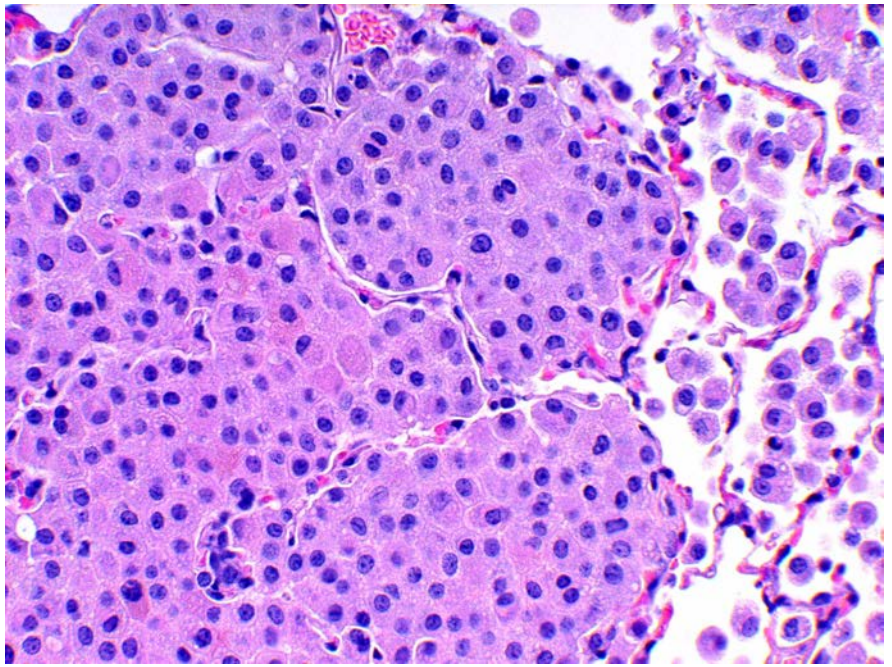






Lesion severity is important in defining an adverse effect





Outline of Presentation

- Definitions
  - Adverse response
  - Adaptive response
  - Reversible response
  - Exacerbation of background lesions
- Communicating Adversity
- Paradigm Shift & Determining Adversity
- Practical Examples of Adverse and Adaptive Responses in Preclinical Studies

Paradigm Shift & Determining Adversity

- In accordance with Tox21 and related global opinion, there is the recommendation to move away from animal testing and to rely on alternative measurements and pathways
  - High throughput screening
  - Toxicity pathways
  - Adversity outcome pathways
  - In vitro testing using human cells
  - Computational systems biology
- Can adverse effects be defined using such new approaches?

Ankley et al., (2010) Environ Toxicol Chem 29:730-41

Paradigm Shift & Determining Adversity

- Use of alternative methods to identify adversity will require establishing scientific validation.
- Until new methods are validated, we continue to rely on classical toxicity testing to identify adverse data for risk assessment.
- Can adverse effects be defined using such new approaches?

  Answer: Not yet.

A Final Definition of Adverse

- In the context of the nonclinical toxicity study, *'…a test-item related change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, animal model, or (sub) population that likely results in an impairment of functional capacity to maintain homeostasis, an impairment of the capacity to compensate for additional challenge, or an increase in susceptibility to other influences.'*
- Based on "apical responses"
  - Clinical signs, lesions, traditional biomarkers
  - And always within the context of a specific study

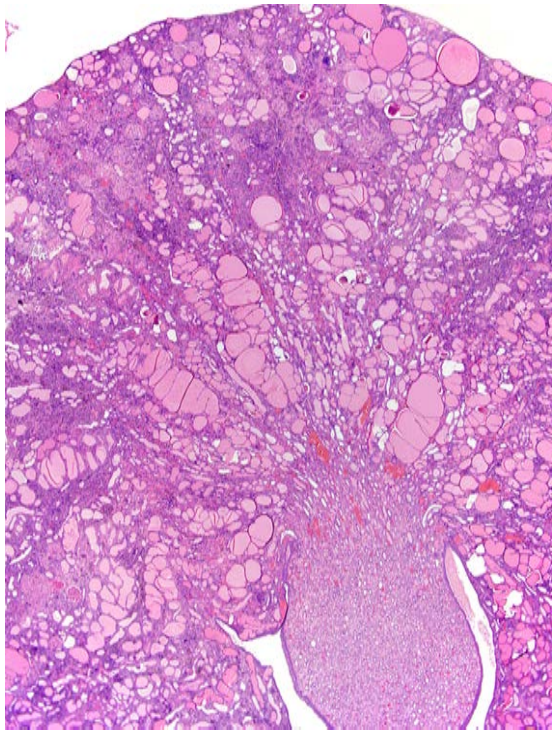
Outline of Presentation

- Definitions
  - Adverse response
  - Adaptive response
  - Reversible response
  - Exacerbation of background lesions
- Communicating Adversity
- Paradigm Shift & Determining Adversity
- Practical Examples of Adverse and Adaptive Responses in Preclinical Studies

Practical Examples

- Restricted to one sex for purposes of demonstrating potential adverse responses
- However, an effect seen in both genders would be of more concern
- Examples are based on reasonably expected study outcomes

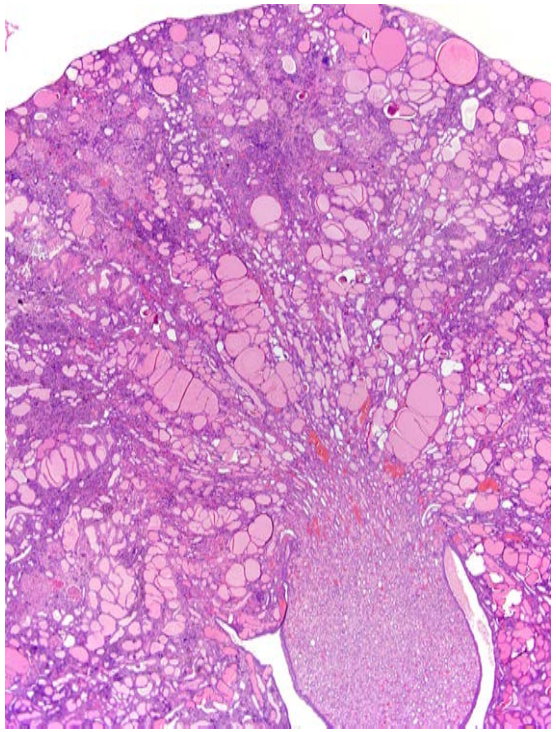
Judgments regarding adversity are controversial. Not everyone will necessarily agree with the following interpretations.



Treatment associated exacerbation of chronic progressive nephropathy

Is this an adverse response?

Sprague-Dawley	12-Month Study			
Microscopic Findings	Control	Low Exposure	Medium Exposure	High Exposure
	n= 20	n= 20	n= 20	n= 20
Chronic Progressive Nephropathy				
% Incidence	10	15	25	30
Minimal	2	3	1	0
Mild	0	0	2	2
Moderate	0	0	2	4
Severity Average	1.0	1.0	2.2	2.7



Treatment associated exacerbation of chronic progressive nephropathy

Is this an adverse response?

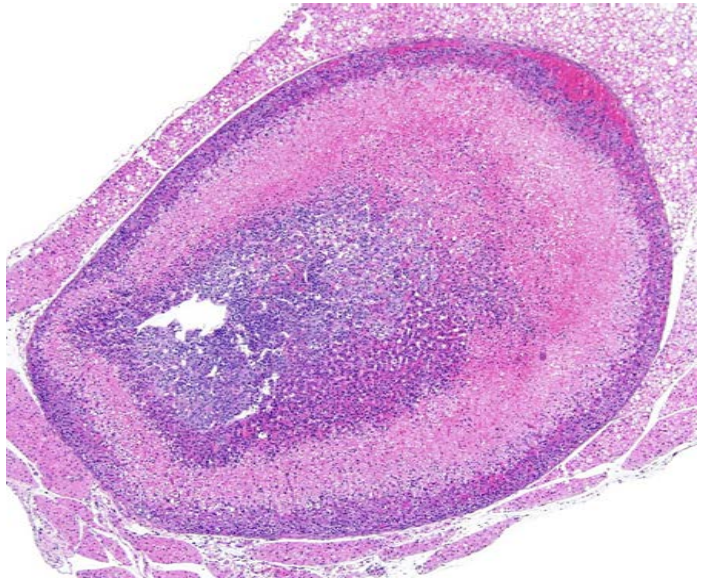
Yes, it is adverse

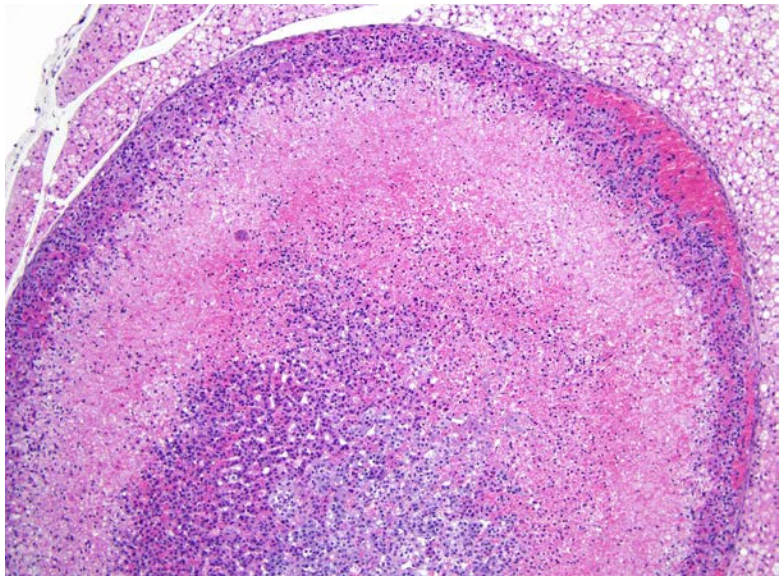
NOAEL

Sprague-Dawley	12-Month Study			
Microscopic Findings	Control	Low Exposure	Medium Exposure	High Exposure
	n= 20	n= 20	n= 20	n= 20
Chronic Progressive Nephropathy				
% Incidence	10	15	25	30
Minimal	2	3	1	0
Mild	0	0	2	2
Moderate	0	0	2	4
Severity Average	1.0	1.0	2.2	2.7

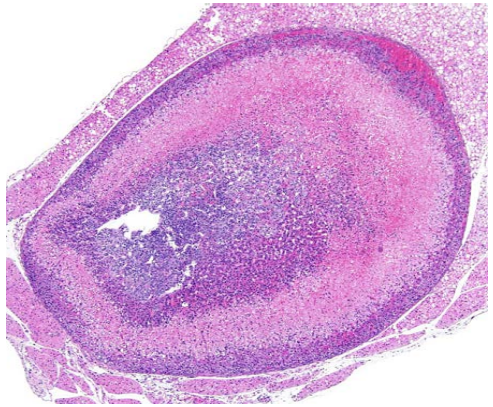
Dose-related increase incidence and increased severity

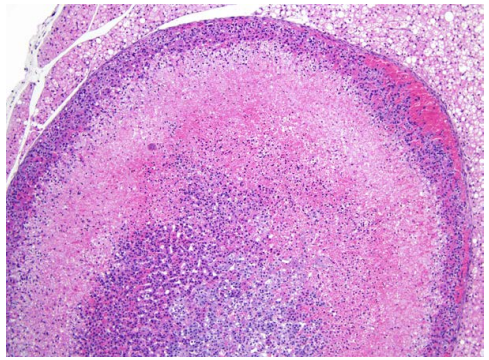
Adrenal Cortical Necrosis





	90-Day Rat Study			
Microscopic Findings	Control	Low Exposure	Medium Exposure	High Exposure
	n= 10	n= 10	n= 10	n= 10
Adrenal				
Necrosis, diffuse, severe	0	0	2	8
Hemorrhage, cortex, focal	0	0	1	6





Adrenal Cortical Necrosis

- Adrenal cortical necrosis is adverse
- The 2/10 incidence at the medium exposure is a severe response

- The NOAEL is the low exposure

	90-Day Study			
Microscopic Findings	Control	Low Exposure	Medium Exposure	High Exposure
	n= 10	n= 10	n= 10	n= 10
Adrenal				
Necrosis, diffuse, severe	0	0	2	8
Hemorrhage, cortex, focal	0	0	1	6

Take Away Messages

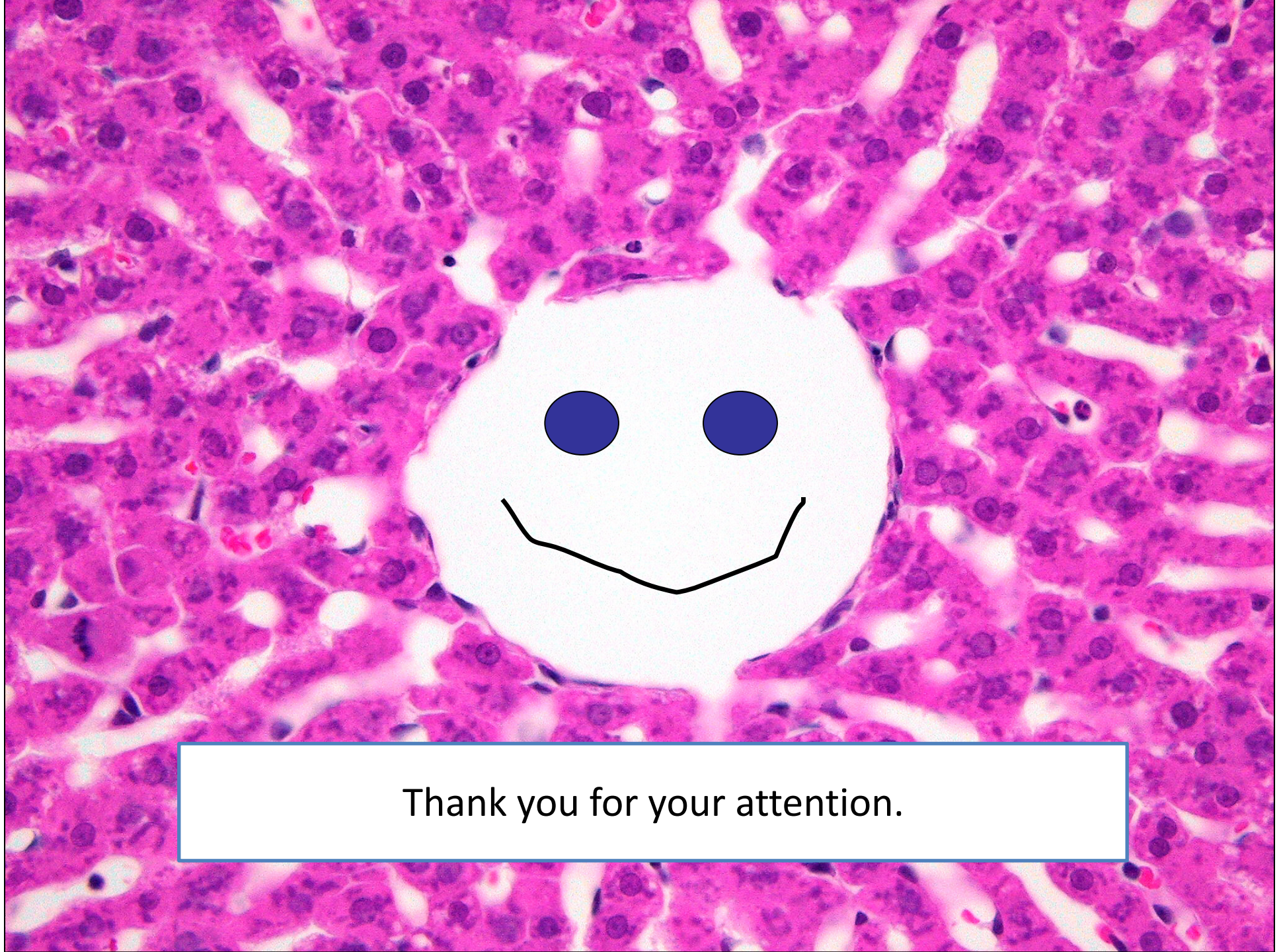
- There is no perfect definition of what is an adverse response in a preclinical study.
- The judgment on the adverse nature of an observation in a non-clinical toxicology study is subject to discussion, challenge, and reinterpretation.

References

- M. A. Dorato & J. A. Englehardt, Reg Tox & Pharmacol (2005) Toxicol Sci 42:265-274
- D.A. Keller et al., (2012) Toxicol Sci 126:291-297
- R. Perry et al., (2013) Toxicologic Pathology 41: 1159-1169
- F. Sewell et al., (2014) Regulatory Toxicology & Pharmacology 70: 414-429
- K. J. Nikula et al., (2014) Toxicologic Pathology 42:472-486
- G. T. Ankley et al., (2010) Environ Toxicol Chem 29:730-41

••••••••••••

- *Scientific and Regulatory Policy Committee: Recommended ("Best") Practices for Determining, Communicating, and Using Adverse Effect Data from Nonclinical Studies*-- Kerlin et al., 2015 Toxicologic Pathology 44(2): 147-62
- *Characterizing "Adversity" of Pathology Findings in Nonclinical Toxicity Studies: Results from the 4th ESTP International Expert Workshop*-- Palazzi et al., 2016 Toxicologic Pathology 44(6): 810-24


Thank you for your attention.