Science Question 4

- **Human relevance of mononuclear cell leukemia**

MNCL is a spontaneous aging lesion occurring at high frequency in F-344 rats

- Spontaneous incidence ranges from 32-74%
  - Tumor data in DINP studies similar to historical averages [22]

Incidence of MNCL from Haseman, [22] Lington, [4] and Moore [5]

	Range of MNCL in controls for NTP feeding studies (Haseman)	Highest incidence of MNCL	
		Lington	Moore
Male	32 – 74%	63.8% (51/80 rats)	49.2% (32/65 rats)
Female	14 – 52%	53.8% (43/80 rats)	46.2% (30/65 rats)

- Many factors affecting tumor frequency unrelated to treatment
  - e.g., dosing methods, caging, diet, vehicle, testing laboratory, etc.
- Species and strain specific
  - Not found in chronic studies in SD rats or in mice

Example of a treatment related vs spontaneous tumor type

Summary for DINP Studies

Organ ▼	Tumor Type ▼	Investigator(s) ▶	Bio\dynamics (1986)		Lington et al (1997)		Moore (1998)		Moore (1998)	
		Strain & Species ▶	S-D Rats		Fischer 344 Rats		Fischer 344 Rats		B6C3F1 Mice	
			male	female	male	female	male	female	male	female
Liver	Combined Adenoma + Carcinoma		NS	S	NS	NS	S	S	S	S
Blood	Mononuclear Cell Leukemia		NR	NR	S	S	S	S	NR	NR

Key:

S	Significant
NS	No Significant Trend
NR	Not Reported / Relevant

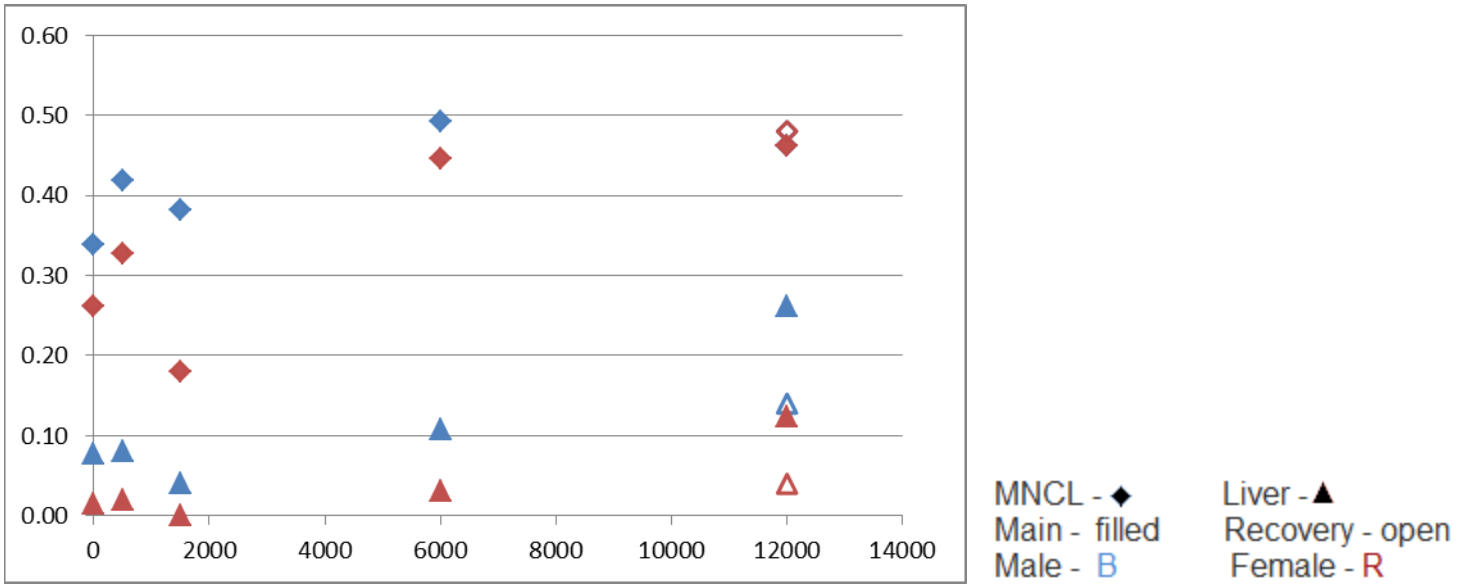
- Liver tumors
  - treatment related
  - consistent across species and strains of rodents
  - defined Mode of Action
- MNCL
  - high spontaneous background incidence
  - species and strain dependent
  - incidence influenced by non treatment factors
  - factor in recommendation that F344-N be discontinued for use by NTP

	Range of MNCL in controls for NTP feeding studies (Haseman)
Male	32 – 74%
Female	14 – 52%

No change in incidence of MNCL in recovery animals

Animals were treated at 500, 1500, 6000, & 12000 ppm in the diet, a recovery group treated at 12000 for 78 wks. then untreated for 24 wks. before sacrifice was included.

Tumor Incidence Moore - Rat



- Liver
  - Decreased incidence in recovery group
  - Consistent with treatment related hypothesis. PPARα-mediated effects would reverse with cessation of treatment
- MNCL
  - equivalent incidence in recovery group
  - Consistent with the hypothesis that these are spontaneous and age-related

The liver tumor data can be modeled but MNCL cannot (i.e., not dose-related)

Summary for DINP Studies

Organ ▼	Tumor Type ▼	Investigator(s) ▶	Bio\dynamics (1986)		Lington et al (1997)		Moore (1998)		Moore (1998)		Lington + Moore	
		Strain & Species ▶	S-D Rats		Fischer 344 Rats		Fischer 344 Rats		B6C3F1 Mice		Fischer 344 Rats	
			male	female	male	female	male	female	male	female	male	female
Liver	Combined Adenoma + Carcinoma		NS	S	NS	NS	S	S	S	S	M	M
Blood	Mononuclear Cell Leukemia		NR	NR	S	S	S	S	NR	NR	**NAM**	**NAM**

Key:

S	Significant
NS	No Significant Trend
NR	Not Reported / Relevant
M	Acceptable Model
NAM	No Acceptable Model

- Liver
  - combined data set can be modeled for BMD
- MNCL
  - combined dataset cannot be modeled for BMD

MNCL is a high frequency aging lesion occurring spontaneously in F-344 rats

- MNCL in the Fischer rat is believed to reflect a high level of spontaneous DNA damage
  - biological plausibility that DINP would act by this mechanism is low
    - uniformly non-genotoxic in both in vitro and in vivo mutagenicity studies including unscheduled DNA repair

- MNCL tumor data from DiNP studies are not treatment specific
  - no change of incidence in recovery animals
  - combined dataset cannot be modeled

- Questionable relevance to humans