Draft NTP Technical Report TR586 on Cimstar 3800 Metalworking Fluid

Daniel Morgan, PhD, DABT
National Institute of Environmental Health Sciences

NTP Technical Reports Peer Review Meeting
May 22, 2014

Metalworking Fluid (MWF) Classes

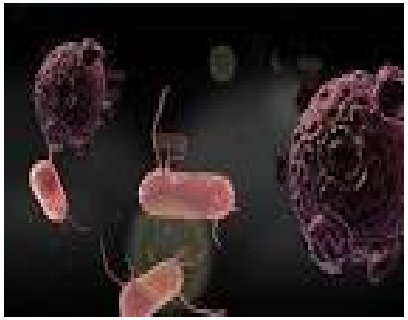
- Oil-based MWFs
  - Straight oils (petroleum or mineral oils) no water
- Water-soluble MWFs
  - Soluble oils (30-85% oil, emulsifiers and blending additives)
  - Semi-synthetic (5-30% oils, hybrid of straight and synthetic)
  - Synthetic (no mineral oils, 70-95% water)

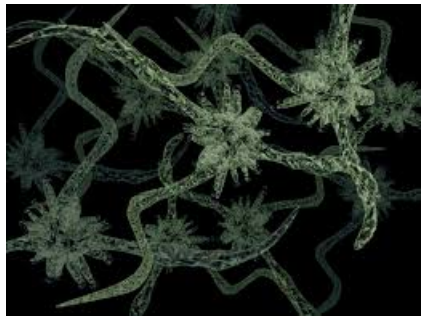
Water-Soluble MWFs (complex mixtures)

- Water (30-50%)
- Anti-foaming agents
- Antioxidants
- Anti-weld agents
- Biocides
- Buffers (alkaline)
- Chelating agents
- Coupling agents
- Corrosion inhibitors
- Detergents
- Dyes
- Emulsifiers
- Extreme Pressure additives
- Lubricity additives
- Plasticizers
- Odorants
- Surfactants

“In-Use” MWF Contaminants

- Metal particles, shavings
- Tramp oils
- Hydraulic fluids
- Bacteria and Endotoxins
- Fungi and Mycotoxins





MWF Nomination & Selection

- **Neat, unused MWFs**
- **Nomination**: NIOSH
- **Selection**: 29 MWFs
  - Estimated production and use: 29 → 18
  - Chemical composition: 18 → 9
  - Class, manufacturer: 9 → 4

MWFs Selected for NTP Studies

- Cimstar 3800 – semisynthetic
- Trim SC210 – semisynthetic
- Syntilo 1023 – synthetic
- Trim VX – soluble oil

NTP Studies on MWFs

MWF	GeneTox	3mo	2yr
Cimstar 3800	√	√	√
Trim SC210	√	√	-
Syntilo 1023	√	√	-
Trim VX	√	√	√

Cimstar 3800 Genetic Toxicity

- E. coli /S. typhimurium
  - Cimstar 3800 was weakly mutagenic in *E. coli* strain WP2 *uvr*A/pKM101 in the absence of S9
  - no mutagenic activity was observed in *S. typhimurium* strains TA100 and TA98 with or without S9, or in the *E. coli* strain with S9
- Micronucleus:
  - There were no increases in the frequencies of micronucleated reticulocytes or erythrocytes in peripheral blood samples from male and female mice or rats exposed to Cimstar 3800 by inhalation for 3 months

3-Month Study Design

- F344/NTac rats and B6C3F1/N mice
- 10 animals/species/sex/concentration
- Liquid aerosols (1.6-1.8 μm MMAD)
- Concentrations: 0, 25, 50, 100, 200, 400 mg/m^3
- 6 hr/d, 5d/wk, 3 months
- Histopathology
- Clinical pathology

3-Month Study Results

	Rats	Mice
Survival:	no effect	no effect
Clin Obs:	nose/eye discharge lethargy, ruffled fur at ≥200 mg/m^3	lethargy, ruffled fur at ≥200 mg/m^3
Body wt:	no effect	↓ at 400 mg/m^3
Lung wt:	no effect	↑ at ≥200 mg/m^3
Clin Path:	no effect	no effect

3-Month Study Results

Histopathology

Nasal Cavity

- Respiratory and olfactory epithelium, hyaline droplet accumulation
  - Present in all exposed rats and most mice
  - Rats: mild - moderate severity
  - Mice: minimal - mild severity
- Goblet cell hyperplasia (rats only)
  - Present in most exposed rats (minimal - mild)

3-Month Study Results

Histopathology

Lung

- Bronchiole, hyperplasia (mice only)
    - Present in all exposed mice (minimal-mild)
- Alveolar histiocytic infiltration
    - Present in male and females rats exposed to 200 and 400 mg/m^3
    - Minimal severity

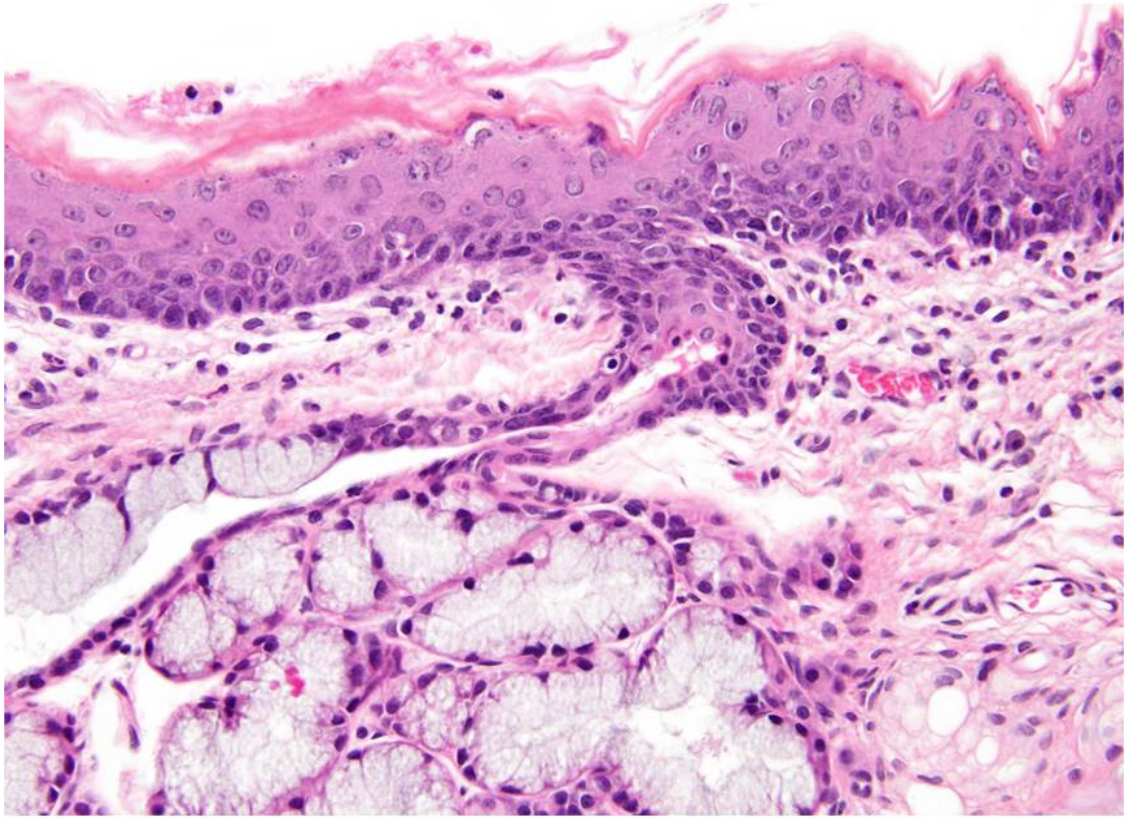
3-Month Study Results

Histopathology

Larynx (most severe lesions)

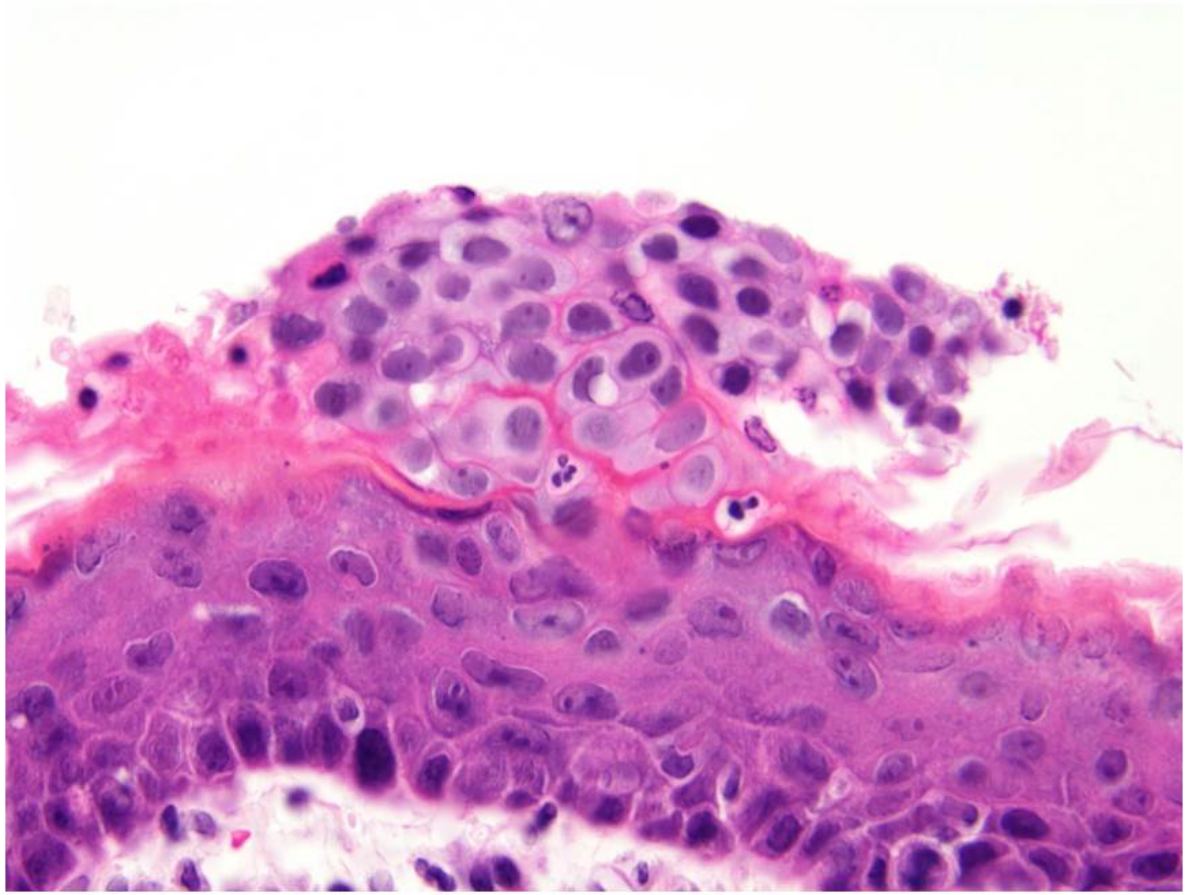
- Respiratory epithelium, squamous metaplasia
  - Present in all exposed rats and mice
  - Rats: marked severity at $\geq$100 mg/m^3
  - Mice: marked severity at $\geq$200 mg/m^3
- Chronic active inflammation
  - Present in most exposed rats and mice
- Squamous epithelium, hyperplasia
  - Present in most mice at $\geq$200 mg/m^3
- Minimal-mild epithelial dysplasia in mice
  - Present in a few male 200 mg/m^3 mice and most male and female 400 mg/m^3 mice

Larynx, epiglottis – squamous metaplasia



Marked squamous metaplasia in a male rat exposed to 100 mg/m^3 Cimstar 3800 for 3 months.

Larynx, epiglottis - dysplasia



Epithelial dysplasia in a male mouse exposed to 50 mg/m^3 Cimstar 3800 for 3 months.

Summary: 3-Month Results

- Nose, larynx, and lung are target sites in rats and mice
- At $\geq$200 mg/m^3
  - Nasal and ocular discharge in rats
  - Increased lung wt and decreased body wt in mice
  - Larynx, marked squamous metaplasia in rats and mice
  - Larynx, minimal-mild epithelial dysplasia in mice
- Exposure concentrations <200 mg/m^3 Cimstar were selected for the 2-yr study

2-Year Study Design

- Wistar Han rats, B6C3F1/N mice
- 50 animals/species/sex/concentration
- Liquid aerosols (1.6-1.8 μm MMAD)
- Concentrations: 0, 10, 30, 100 mg/m^3
- 6 hr/d, 5d/wk, 104 wk
- Histopathology

2-Year Study Results: Rats

- Survival
  - No effect on male or female rats
- Body Weights
  - No effect on male or female rats

Male Rats: Neoplastic Lesions

PROSTATE Concentration (mg/m^3):	0	10	30	100
Adenoma including multiple	1/50	1/50	1/50	3/50
Carcinoma	0/50	0/50	1/50	0/50
Adenoma or carcinoma	1/50	1/50	2/50	3/50 [a]

[a] p= 0.304
[b] Historical control incidence for all routes of 2-year studies: 1/150

Male Rats: Neoplastic Lesions

BRAIN Concentration (mg/m^3):	0	10	30	100
Granular Cell Tumor, Benign	0/50	2/50	0/50	1/50
Granular Cell Tumor, Malignant	0/50	1/50	1/50	0/50
Granular Cell Tumor, Benign or Malignant [a]	0/50	3/50[b]	1/50	1/50

[a] Historical control incidence for all routes of 2-year studies: 3/150
[b] p= 0.116

Male Rats: Select Nonneoplastic Lesions

NOSE Concentration (mg/m^3):	0	10	30	100
Hyperplasia, Goblet Cell	0/50	20/50**	25/50**	34/50**
Olfactory Epith – Hyaline Droplet Accumulation	19/50	50/50**	50/50**	50/50**
Olfactory Epith – Glands, Hyperplasia	1/50	39/50**	47/50**	50/50**
Respiratory Epith – Hyaline Droplet Accumulation	0/50	17/50**	25/50**	29/50**
LARYNX				
Metaplasia, Squamous	1/50	47/50**	50/50**	50/50**
LUNG				
Inflammation, Lymphohistiocytic	6/50	14/50*	41/50**	47/50**
Alveolar Epithelium - Hyperplasia	4/50	6/50	11/50	13/50*
LYMPH NODES				
Bronchial – Hyperplasia, Lymphohistiocytic	0/42	0/40	10/37**	28/35**
Mediastinal – Hyperplasia, Lymphohistiocytic	0/46	0/45	4/50	29/49**

* Significantly greater than control, $p \leq 0.05$; **$p \leq 0.01$

Female Rats: Neoplastic Lesions

SKIN Concentration (mg/m^3):	0	10	30	100
Squamous Cell Papilloma	0/50**	0/50	0/50	3/50
Squamous Cell Papilloma, Papilloma, or Keratoacanthoma [a]	0/50*	0/50	0/50	4/50 [b]

[a] Historical control incidence for all routes of 2-year studies: 0/150
[b] *p*=0.063
* Statistically significant trend (p<0.002; ** p<0.008)

Female Rats: Neoplastic Lesions

Concentration (mg/m^3):	0	10	30	100
Uterus – Original Sections				
Adenocarcinoma or MMMT [a, b]	1/50	1/50	1/50	3/50
Uterus – Residual Longitudinal Sections				
Adenocarcinoma or MMMT [c]	0/50	4/50	5/50*	6/50*
Uterus – Original or Residual Longitudinal Sections (combined)				
Adenocarcinoma or MMMT	1/50	4/50	5/50	6/50

[a] Historical control incidence for all routes of 2-year studies (adenocarcinoma only): 7/150
[b] MMMT = Mixed malignant Mullerian tumor
[c] Adenocarcinoma incidence in controls from other reviews of longitudinal uterine sections in Wistar Han rats (original or residual sections combined): 4/50, 8/50
* Statistically significant ($p<0.05$)

Female Rats: Select Nonneoplastic Lesions

NOSE Concentration (mg/m^3):	0	10	30	100
Hyperplasia, Goblet Cell	0/50**	25/50**	34/50**	42/50**
Olfactory Epith – Accumulation, Hyaline Droplet	16/50**	50/50**	50/50**	50/50**
Olfactory Epith, Glands – Hyperplasia	1/50**	32/50**	48/50**	49/50**
Respiratory Epith– Accumulation, Hyaline Droplet	1/50**	24/50**	31/50**	34/50**
LARYNX				
Metaplasia, Squamous	1/50**	50/50**	50/50**	50/50**
LUNG				
Inflammation, Lymphohistiocytic	3/50	20/50**	42/50**	50/50**
LYMPH NODES				
Lymph Node, Bronchial – Hyperplasia, Lymphohistiocytic	0/38**	0/35	7/32**	30/35**
Lymph Node, Mandibular – Hyperplasia, Lymphohistiocytic	0/49**	0/46	4/45	23/47**

** Significantly greater than control, $p \leq 0.01$

Male Mice: Neoplastic Lesions

- There were no treatment-related increases in the incidence of neoplastic lesions in male mice

Male Mice: Select Nonneoplastic Lesions

NOSE Concentration (mg/m^3):	0	10	30	100
Nose, Olfactory Epithelium - Hyaline Droplet	4/50	31/50**	43/50**	49/50**
Nose, Olfactory Epithelium - Metaplasia, Respiratory	7/50	15/50*	25/50**	37/50**
Nose, Respiratory Epithelium – Hyaline Droplet	7/50	36/50**	50/50**	50/50**
LARYNX				
Larynx – Inflammation, Chronic-Active	0/50	2/50	3/50	8/50**
Larynx – Metaplasia, Squamous	0/50	50/50** [1.0]	49/49** [2.0]	50/50** [3.4]
LUNG				
Lung, Bronchiole – Hyperplasia	11/50	11/50	32/50**	44/50**
Lung, Alveolar Epithelium – Hyperplasia	4/50	4/50	6/50	7/50

*Significantly greater than control, $p \leq 0.05$; **$p \leq 0.01$
[severity grade] where 1 = minimal, 2=mild, 3=moderate, 4= marked

Female Mice: Neoplastic Lesions

LUNG Concentration (mg/m^3):	0	10	30	100
Alveolar/ Bronchiolar Adenoma	1/50	4/50	2/50	4/50
Alveolar/ Bronchiolar Carcinoma	4/50*	1/50	4/50	8/50 [a]
Alveolar/ Bronchiolar Adenoma or Carcinoma	4/50**	5/50	6/50	12/50*[b]

* Significant trend $p \leq 0.05$; **$p \leq 0.01$

[a] Exceeds historical control range – same route 0-10%, all routes 0-14%

[b] Exceeds historical control range – same route 2-16%, all routes 2-22%

Female Mice: Neoplastic Lesions

THYROID GLAND Concentration (mg/m^3):	0	10	30	100
Follicular Cell Carcinoma	0/50**	0/48	0/50	3/50 [a]

** Significant trend p≤0.008

[a] Exceeds historical control incidence: 2/942

Female Mice: Select Nonneoplastic Lesions

NOSE Concentration (mg/m^3):	0	10	30	100
Olfactory Epithelium – Hyaline Droplet	25/50	40/49**	50/50**	49/50**
Olfactory Epithelium – Metaplasia, Respiratory	3/50	4/49	12/50*	23/50**
Respiratory Epithelium – Hyaline Droplet	34/50	48/49**	50/50**	50/50**
LARYNX				
Inflammation, Chronic-Active	0/49	0/49	0/50	10/50**
Metaplasia, Squamous	1/50 [1.0]	49/49** [1.1]	50/50** [2.1]	50/50** [3.5]
LUNG				
Bronchiole – Hyperplasia	7/50	4/50	22/50**	41/50**
Alveolar Epithelium – Hyperplasia	4/50	2/50	5/50	4/50

Significantly greater than control, $p \leq 0.05$; **$p \leq 0.01$
[Severity grade] where 1 = minimal, 2=mild, 3=moderate, 4= marked

Cimstar 3800: Conclusions

- Male Rats: **Equivocal Evidence**
  - based on the incidences of prostate gland adenoma or carcinoma (combined) and benign or malignant granular cell tumors (combined) of the brain.
- Female Rats: **Equivocal Evidence**
  - based on the incidences of squamous cell papilloma and keratoacanthoma (combined) of the skin, and adenocarcinoma or mixed malignant Mullerian tumor of the uterus.
- Male Mice: **No Evidence**
- Female Mice: **Some Evidence**
  - based on the incidences of follicular cell carcinoma of the thyroid gland and alveolar/bronchiolar adenoma or carcinoma (combined) of the lung.