

Reflections on 40 Years Of Industrial Toxicology in the Pharmaceutical Industry

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Occupational Toxicology Roundtable (OTR)
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Dennis Paustenbach, PhD, DABT, CIH

- 1970-1974: Chemical engineer who minored in Environmental Engineering
- 1971 (Summer): Fire protection engineer
- 1972 (Summer): Air pollutant engineer
- 1973 (Summer): Industrial Hygiene Trainee

Note: Birth of environmental movement was 1970 (Earth Day)



Historical Experience

- 1974: B.S. in Chemical Engineering
- 1974-1977: Eli Lilly & Co. (also DOW intern)
- 1977: M.S., University of Michigan (IH & Tox)
- 1978: Helped put together one of the first occ tox programs in Pharma Industry
- 1975-1980: Attended Warren Cook Symposia (IH) and some Selby Conferences (Occ. Med.)

My Relevant Experience

- 1978- 1980: Eli Lilly & Co. (IH engineer and manager)
- 1979-1982: Pursued PhD in toxicology (taught 300 undergrads)
- 1982-1984: Stauffer Chemical (tox & risk assessment)
- 1984-1987: Syntex Pharmaceuticals (tox & risk assessment)

Historical Experience

- 1987-2020: Consultant in toxicology and risk assessment (Founder of 125 person firm in tox and risk assessment)

-Eli Lilly

-Hewlett Packard

-Kodak

-3M and MSA

-Johnson and Johnson

-Almost 100 of Fortune 300 firms



My Charge and Challenge

- Eric and others asked me to share a retrospective with the group
- To review the early years of IH and Tox in the Pharma and their Ag Chemical business
- To discuss case studies that still might be informative

My Challenge

- Alert you to “state of the art” defenses with respect to litigation (e.g., juries place heavy emphasis on corporate conduct)
- But to share ideas still relevant in 2020
- Look into crystal ball

Overview

- My impressions of this gathering
- Early years in Pharma
- Some case studies
- The role of plaintiff bar and litigation in the post-1980 era
- Looking into the future

Impressions of This Gathering

- Considerable focus on setting OELs (the work was impressive)
- Some discussion of IH aspects (gloves, procedures, etc.)
- The future use of in-vitro, in-silico, and other testing (research without animals)

Early Years in Pharma IH & Tox

- Dow/DuPont “set the bar” (1945-1985).
- Earliest Occ Med and Industrial Hygiene programs in Pharma began around 1955
- Relationship with the pharm/tox group was minimal (quite distant)
- Often within the human resources and/or safety department (1968-1985-present)
- In general, most professionals and governments considered pharma to be super clean (e.g., a pill producer).



Early Occ Medicine Departments in Pharma (1950s-1960s)

- Handled cases in-house
- At Selby discussion, information was traded
- Prevention was the focus
- Also emphasized engineering controls and personal protective equipment.



CAREY P. MCCORD
1886-1979

Early Years

- Beryllium caught everyone by surprise (1948)
- Mesothelioma was unexpected (1964) [but a dusty industry]
- BCME, Benzene (1976), vinyl chloride (1974) changed everything
- They were invisible, non-odorous, non-irritating vapors causing fatal cancers
- All of industry (including pharma) was a bit shocked

An Environmental Odyssey

*People,
Pollution,
and Politics
in the Life of
a Practical
Scientist*



Occupational Carcinogen Surprises (1948-1975)

- Benzidine and bladder cancer
- BAP and coke ovens (lung cancer)
- Cadmium (kidney cancer)
- Asbestos and insulators (meso)
- Radium (lung cancer)
- CR VI via inhalation (lung)
- Benzene and AML



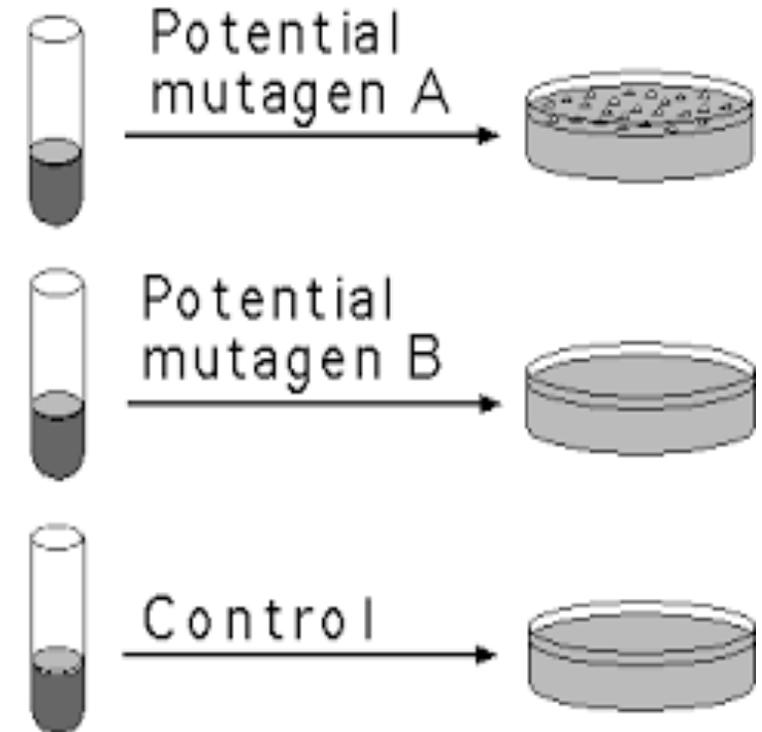
**1971 - PRESIDENT NIXON
DECLARES "WAR ON CANCER"**
Launching a \$1.6 Billion (US)
dollar crusade.

The Passage of OSHA (1970)

- Sort of caught the pharma industry by surprise.
- Nonetheless, the industry didn't believe they had many occupational health hazards.
- We conducted dozens of baseline studies using “professional judgement” (consultants, other than insurance companies, were virtually non-existent) and many air samples.

The Ames Test Changed Everything (1971-1976)

- Everyone was searching for a way to identify carcinogens without using the 2-yr bioassay
- Ames test alerted us to the importance of mutagens (1975)
- This changed everything and it brought pharmacologist/toxicologists into routine contact with Occ Med and IH (circa 1975)



Pharma Industry (1970-1990)

Early Names in I.H. in Pharma (1970s)

- Paul Woolrich: Upjohn
- Herb Walworth: Kemper/pharma
- Tom Yoder: Eli Lilly
- Larry Hecker: Abbott
- Ed Sargent: Merck

Early History

- In 1960, in the U.S., there were no genuine industrial hygiene programs in most of the pharma industry.
- Indeed, it was considered the “cleanest and safest” industry in America (pre 1965) by outsiders.



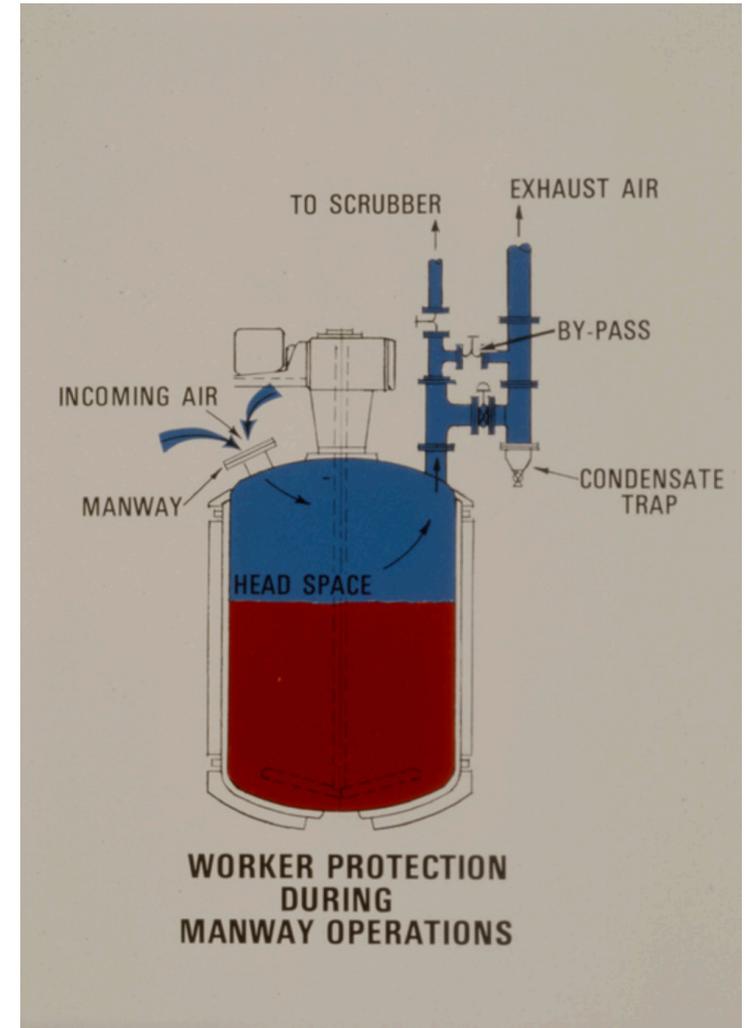
The Dow “product stewardship” program (1975)

- At Eli Lilly, we wanted to purchase 1,1,2-TCE from Dow.
- To purchase it, due to its high toxicity, Dow insisted that we have an IH program at the facility.
- None of our manufacturing sites had an IH (only corporate).
- Not unusual at the time.



Most “Outsiders” Did Not Know Pharma Used Batch Chemical Manufacturing Facilities (1970-1990)

- This surprised the early OSHA inspectors (who generally only went to final product packaging and handling)
- They did not know what they were missing....



Early Results of the Baseline Studies (1975-1982)

- The industry began discussing what was being learned (as we are doing this week).
- Much discussion about complying with the TLVs (much less about PEL).
- Not surprisingly, it was the classic historical IH chemicals that were of concern (not pharma products).
- The no warning properties, acutely toxic, and dermal risk chemicals captured everyone's attention.

Results of the Baseline Surveys (1975-1982)

- Usually below OSHA PEL, but not always
- For 80% of chemicals, the TWA was below PEL and TLV
- Then, we wondered about adopting Liedel and Busch (1978) sampling programs



Pharma Took OSHA Seriously (1974-1984)

- Tens of millions were spent on sampling workers.
- Engineering controls were the first line of defense.
- Respirators and gloves were important.

State of the Art (Pharma and Occ Health)

- Although a little late in the game, pharma quickly caught up to the major chemical firms (perhaps, in less than 12 years) in industrial hygiene, occ med and occupational toxicology.
- The emphasis on good employee morale and healthfulness was always very high (1950 to the present).
- Understanding pioneering efforts is probably useful from a litigation standpoint.

The Industry was Focused on
Pushing the Boundaries

Pushing Back Threats of Litigation

- Have your “good conduct” story in order
- Juries want to understand corporate attitudes
- Called a “state of the art” defense

Interesting Trivia (air sampling) (1974-1980)

- Eli Lilly and Monsanto worked together to markedly improve the sensitivity and accuracy of air sampling
- Both developed the jumbo charcoal and silica gels tubes manufactured by SKC around 1977
- Both advanced the ball on collection tubes with GC packing and thermal desorption (getting to ppt levels by 1980)
- Early SKC pumps were beta tested at Eli Lilly and Upjohn (1975-76)



New Sampling and Analytical Chemistry Capabilities (1974-1980)

- Charcoal and silica gel tubes generally replaced impingers.
- Progressed from 30 min area samples to 8 hour personal samples.
- The GC, then GC-EC, then GC-MS allowed 1 ppm and lower detection limits.

Interesting Trivia (engineering controls)

- Several pharma firms invested tens of millions in specialized local exhaust ventilation capture hoods
- Extensive “effectiveness of control” work was conducted to insure controls were working
- Convened among first meetings featuring controls for batch chemical and/or pharma processing (Traverse Bay, Michigan (1979))

Interesting Trivia (gloves)

- Several glove companies beta tested different gloves for different uses in the pharma industry
- Pharma firms applied their typical “detailed approach” to science by conducting glove “break-through studies” with many, many different chemicals (late 1970s)



Interesting Trivia (respirators)

- 3M 8710 was beta tested at Eli Lilly (maybe elsewhere)...and two strap system was implemented
- Other “paper masks” were evaluated
- In the mask “protection factors” were measured rather than assumed
- A myriad of air supplied hoods were field tested and validated

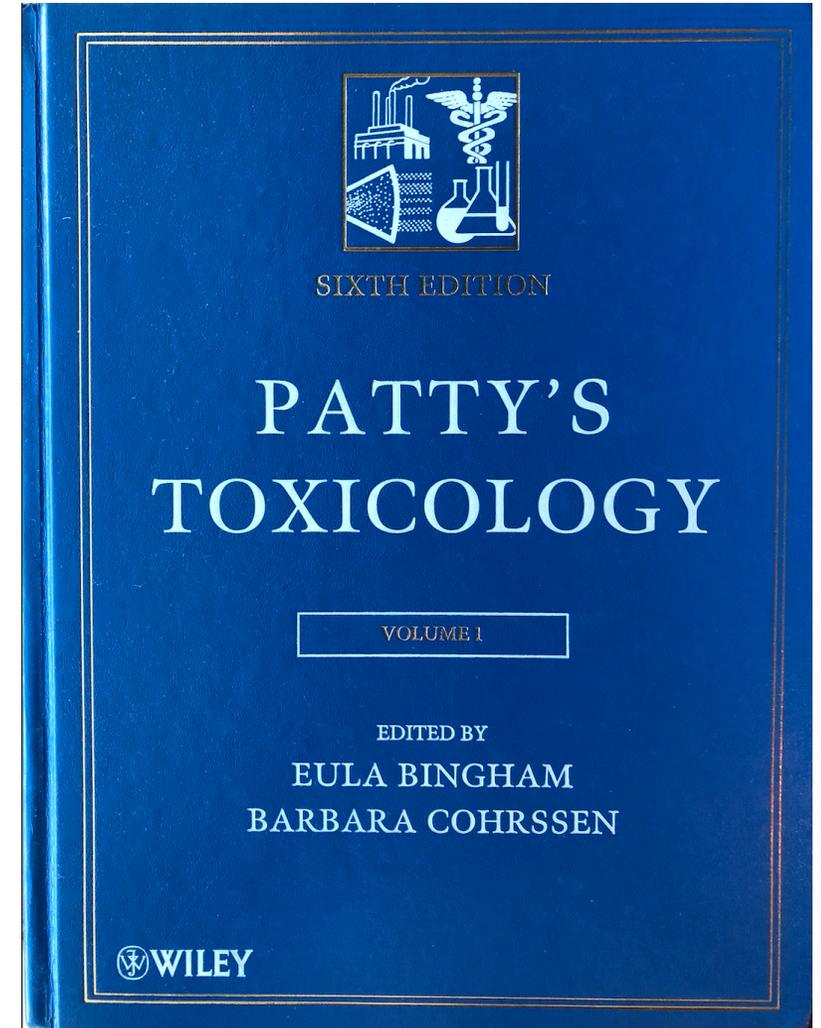


Interesting Trivia (aggressive air sampling programs)

- Again, due to sensitivity to science issues and statistical power, as well as the release of Liedel and Busch (1976) guidelines, the classic annual or routine “campaign” approach was not used
- Some facilities had daily sampling of one, two or three persons in each job exposure groups (JEG)
- Began to issue monthly reports per process with statistical interpretation of data by 1980-1982 (and shared with employees)

Early OELs in Pharma (1978-1980)

- This was a difficult management decision.
- If you set OELs, were you placing your firm at risk of general duty clause infractions or did the possible benefits to worker outweigh legal exposure?
- It took nearly a year but most firms, by 1980, decided that worker health superseded concerns about OSHA or trial lawyers; so OELs were set.
- Methods today are not dramatically different than in 1980; although they feel much more complicated.
- Safety factors remain in the range of 50-500 for most chemicals.



Confluence of the Ames Test With a
True Desire to Ensure Employee Safety
(Recognition that Pharma Didn't Just
Package Pills)....Changed the
Landscape Between 1976-1980

Toxicity of Some Drug Intermediates...“some surprises”

- Around 1974-1977, several firms noted that the isolated intermediates were causing various maladies in workers (skin/eye irritation, respiratory sensitization, elevated liver enzymes, etc.)
- Results of some acute tox studies were sometimes troubling
- When challenged in Ames Test; there were more than a few surprises.
- Soon thereafter, many pharma firms began assigning tox/pharm staff to focus on occupational hazards.

Raised Awareness Brought Us Together

- My recollection is that perhaps the first meeting like this one (e.g., occupational toxicologists in pharma) occurred around 1978 (perhaps covered by Ed Sargent of Merck)
- Then, every couple years, we got together informally to share our experiences.



The Manufacturing and
Packaging Operations Produced
Some Interesting Case Studies
(1965-1995)

Ten Case Studies

- Beryllium (1948)
- Occ Dermatitis (1955-1995)
- Blotching of skin
- Take home exposure
- Hazards posed by eye irritants
- DMF and Alcohol (1975)
- Respiratory Irritants and Sensitizers
- Vinyl Chloride (1975)
- Benzene in Laboratories
- Agricultural Chemicals (1975)
- The Challenges of Sensitizers

Case Study # 1: Beryllium in Cleveland

- Basically a foundry environment
- Three groups of workers appeared
 - Those who had breathing problems within 10 days (ABD)
 - Those who worked 2-10 years and became sensitized and developed granulomas
 - Group three developed CBD sometime in their career (which could be fatal)

Beryllium...Insight About the Future in Pharma

- Pregnant women seemed more susceptible (1949)
- The doses for all three diseases appeared dependent on polymorphisms (not accepted within the tox community until 2000-2010)
- Today, the pharmaceutical industry, more than any other, is aware of differences in individual susceptibility and genetic predisposition

A Window into the Future of Occupational Toxicology in Pharmaceutical Industry

- Most incidents would be person specific responses
- Asthma, dermal and ocular irritation, lung disease, and systemic disease

Case Study #2: Occ Dermatitis (1955-1995)

- Unexpected dermatitis problems
- These were numerous because the potency of the pure synthesized material was often underappreciated
- Read books by Birmingham, Adams , Maibach, Marks, and others on occ dermatitis
- Frequently, an idiosyncratic response

Case Study # 3: Blotching of the Skin (circa 1965)

- In manufacture of certain drugs, we observed depigmentation of the skin of African Americans.
- It appeared to be due to contact with the skin, it also appeared possible due to systemic intake.
- Developed novel wipe sampling techniques.
- Removed quite a few persons from these operations.

Case Study # 4: Take Home Exposure (circa 1965)

- Father of young girl works in manufacturing of hormones.
- He used one of the first dual change rooms in the nation.
- Showered at end of each day.
- All garments including underwear and shoes were left on-site.

Take Home Exposure

- 8 year old daughter develops breasts prematurely
- She begins to menstruate
- Father works in DES production but he has no symptoms of over-exposure

A Quiz for This Audience...

- It was suspected that some of the DES was getting home.
- How did this happen?
- There was a removal of clothing and a shower occurred.
- All clothing (including underwear) was laundered every day.

Answer

- It appears that the wristwatch was used at work was passed through the change room
- Daughter enjoyed playing with the “twist-a-flex” watch band of the 1960’s
- Enough of the potent pure pharmaceutical was in the flexible watch band to get on daughter’s hand and was ingested

Case Study # 5: Eye Irritants (1960's-1970's)

- Certain pharma agents while packaging, would cause eyes to swell (mostly in women).
- Local exhaust ventilation, in other direction, was used (wrong application).
- To fix the problem, the last steps of packaging were conducted in sequential lab hoods.

Case Study # 6: DMF and Alcohol (1975)

- Employees were exposed to dimethyl formamide (DMF) in air at the TLV
- This was part of Keflex and other drug syntheses
- There was probably some skin contact with DMF
- Following the typical “end of day” beer, some employees had labored breathing or skin blotching (hands and face)
- My first discovered “occ disease”

DMF and Skin Absorption

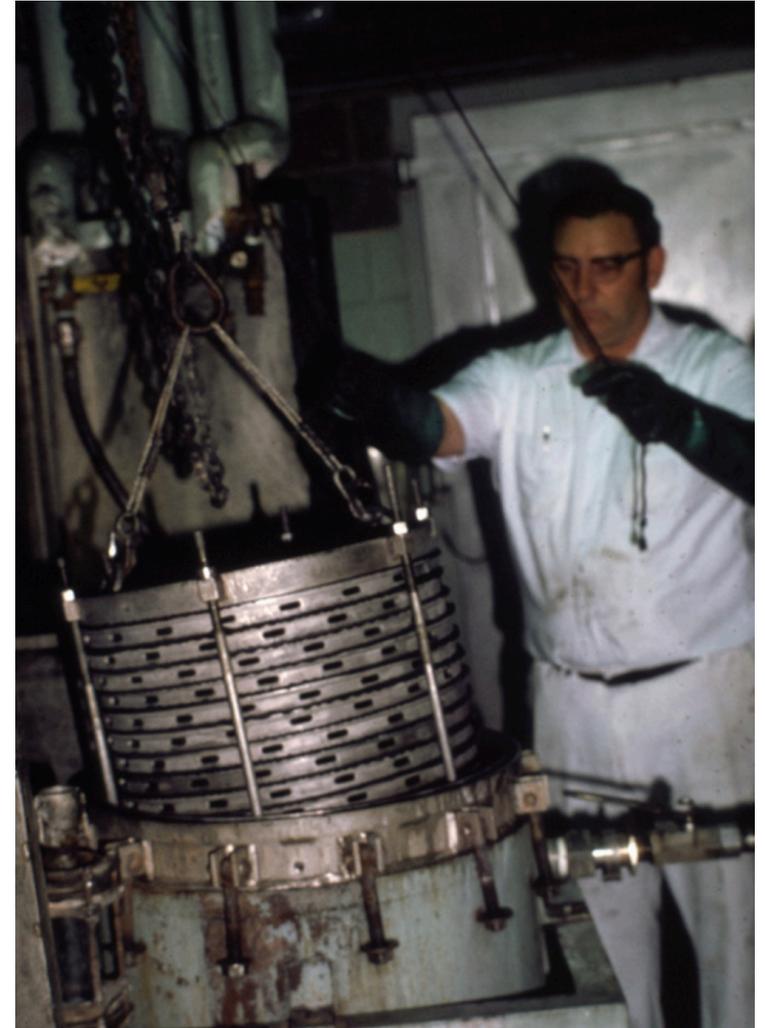
- DMF had, even in 1970, a skin designation (a sister to DMSO)
- We conducted a study on dogs (DMF and ethanol).... and observed same response
- Proposed mechanism was published in journal
- This permanently cemented the occupational toxicologist to the Industrial Hygiene and Occ Med Team

Case Study # 7 Respiratory Irritants and Sensitizers (1970s-1980s)

- A big problem when producing and drying high volume final products (pharma and ag).
- The large molecules suggested that they could be sensitizers as well.
- Chronic stuffy nose, runny nose, throat and upper respiratory tract irritation was common.
- At another facility of 400 persons, more than 100 had to find different jobs. At a facility of 600, persons almost 200 were relocated on site.

Case Study # 8: Vinyl chloride (VC) (1975)

- VC was not used in the pharma industry but it was soon found in exhaust air (as an off-gas of syntheses)
- Then a workplace evaluation followed
- Interestingly, we detected VC at ppb concentrations in some workplaces



Case Study # 9: Benzene in Laboratories

- In 1970s, some drugs were still studied using paper chromatography in bell jars filled with benzene!
- Concentrations in the lab were way higher than expected.
- We biomonitored blood and urine.
- Detected early liver disease and WBC changes in some workers.

Benzene in Labs

- We moved paper chromatography to hoods.
- Adopted daily 8 hour TWA sampling in Labs.
- Tried to substitute toluene for benzene.
- Began an industry-wide discussion about many substituting many chemicals

Case Study #10: Agricultural Chemicals

- Remember, by 1970, Pharma had branched into Agricultural Chemicals and were major players.
- Eli Lilly, in particular, made Tylosin (pig pharma), Treflan (soy bean herbicide), Monensin (chicken pharma), and others.
- These were bulk chemicals (many tons produced per day).

Agricultural Chemicals

- In one location, one year after production, an employee a week complained of a bloody nose and nasal congestion. We moved him to another job.
- Within twelve months, we “burnt through” (a health physics term) about 40 persons at that packaging facility.
- Was eventually “helped” by enjoying controls and fixed by air-sampled hoods.

Case Study #11: The Challenges of Sensitizers (1978-Today)

- Obviously, the isocyanates alerted industrial hygiene about the hazard.
- Some pharma agents required specific engineering controls like the isocyanates.
- Some sites seemed permanently contaminated!
- In some cases, manufacturing had to be isolated and entered only in space suits.

Possible Solution

- I recommended removing any non-essential equipment, then steam cleaning all walls, ceilings and floors
- Then spray paint facility all white with epoxy paint
- This created a new, visually clean and well lit environment to work for manufacturing employees.
- The employees worked every day to keep it white and steamed it down after every shift.
- It worked.

Interestingly...

- After presenting this case study at an AIHC, Kodak quietly told me they had the same problem with silver (which causes argyria)
- They retained me.
- We implemented this approach.
- It worked.

Looking ahead (2020-2035)

Predictions (2020-2035) (OELs)

- Continued pressure on lowering OELs.
- NIOSH decision to move PEL down to risk of 1 in 10,000 for caregivers is significant (if implemented).
- Expect OELs on irritants to be most impacted.

Predictions (2020-2035)

- The plaintiff bar will continue to focus on pharma. At some point they will focus on subcontractors in production.
- Talc, hip implants, mesh, and suntan lotion should be an omen.
- Setting OEL continues to be wise; as long as you meet them.

Predictions 2020-2035

- Better analytical chemistry will help with characterizing exposure
- Improved biological monitoring is inevitable
- Better techniques for wipe sampling (surface and skin) will evolve and wipe criteria will be more common.
- Subtle biomarkers may "haunt" pharma and chemical industry (some will be uninformative)

Predictions 2020-2035

- More concern about take home exposure is likely.
- More concern regarding release of agents to ambient air and water (e.g., community exposure).

Predictions 2020-2035

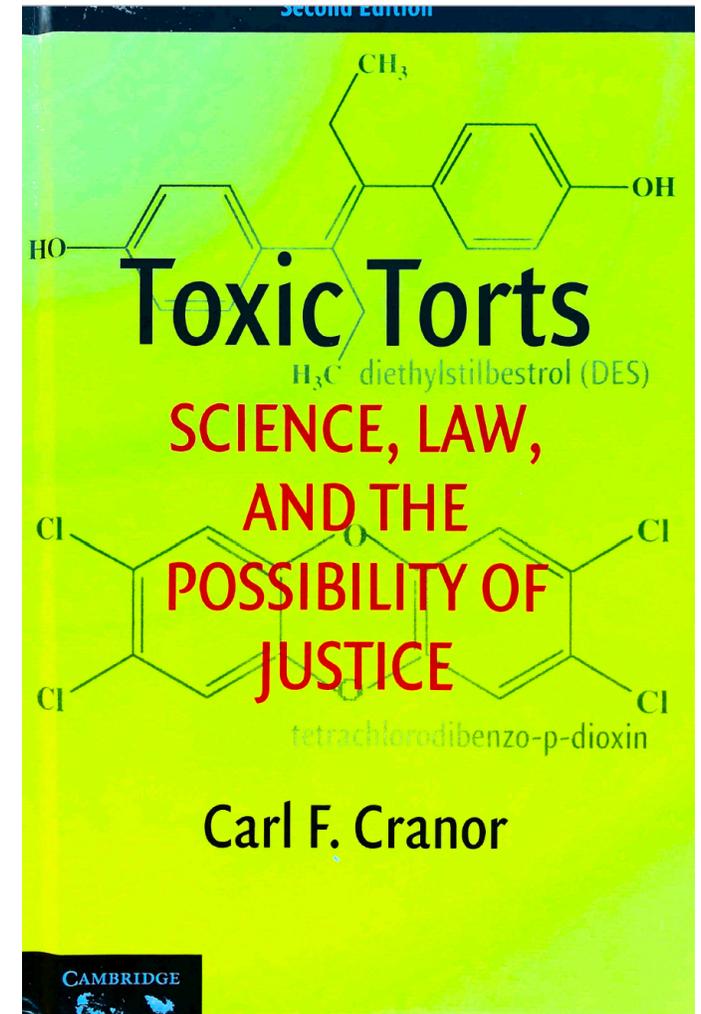
- The pressure not to use animals will continue
- Our experience in this space, using computers and bacteria, is still emerging
- It is unlikely that these approaches will guarantee protection equal to an animal study
- The human response is hugely complex, due to redundant compensatory mechanisms

Predictions 2020-2035

- Claims will likely be leveled about persons living within a couple blocks of pharmaceutical manufacturing facilities
- Plaintiff's bar has pursued asbestos manufacturers, beryllium facilities and steel mills

Predictions 2020-2035

- Over past 10 years, there have been some claims of exposure to “toxic” pharmaceuticals by contractors who work in manufacturing facilities
- These craftsmen (electricians, pipefitters, insulators, etc.) file “premises” cases since employees are barred by worker’s comp.



Corporate America and Pharma

- In 1975, the mantra in pharma was “we will be responsible but not the leaders”
- In 2019, one of the largest pharma firms recently told me, we will be responsible, but not be seen as “out front”.
- It is curious to me, as a 35 year Silicon Valley resident, when firms don’t want to be seen as disruptive and leaders.

Final Thought

- I am happy to give this talk to senior management, inside counsel or outside counsel.
- They might find it useful.