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HEALTH EFFECTS OF PROJECT SHAD CHEMICAL AGENT:

ZINC CADMIUM SULFIDE

[CAS#s 12442-27-2, 68583-45-9]
[11129-14-9, 8048-07-5]

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SPECIAL NOTE ON PSYCHOGENIC SEQUELAE OF PERCEIVED EXPOSURE TO BIOCHEMICAL WARFARE AGENTS

This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates, by reference and attachment, a supplement entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress experienced personally from actual or perceived exposure to chemical and biological weaponry. Because awareness of exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic health consequences of perceived exposure may be regarded as additional health effects arising from the exposure to Project SHAD agents. This reasoning may also apply to simulants and tracers. Therefore, a general supplement has been created and submitted under this contract to address possible psychogenic effects of perceived exposure to biological and chemical weaponry.

Because such health effects are part of a recent and growing public concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.

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I. EXECUTIVE SUMMARY

Zinc cadmium sulfide (ZnCdS) is a brightly fluorescent, stable compound formed by sintering ZnS (zinc sulfide) and CdS (cadmium sulfide). ZnCdS has several CAS (Chemical Abstract Service) registry numbers. It is used in pigments, and its fluorescence is employed as a visualization agent for applications such as histology and nanotechnology. It was used in Project SHAD as a tracer for chemical and biological warfare agents because it was regarded to be a harmless dye.

Very little is published about its health effects. What little there is suggests minimal toxicity. Older studies found that ZnCdS did not induce deaths in dogs or rats despite extraordinarily high oral doses. No epidemiological, clinical, or case studies demonstrating deleterious effects from exposures were found. Personnel who had been most exposed during tests of the compound in the United Kingdom (UK) did not show unusual or discernible health consequences.

The National Research Council (NRC) published a book-length report in 1997 on ZnCdS toxicity arising out of public concern over the exposure of civilian populations to the compound during US Army biological warfare testing in the 1950s and 1960s. The NRC found little literature existing on the subject and concluded that toxic effects of the compound are highly unlikely as the substance is insoluble and very unlikely to become bioavailable. Nonetheless, the NRC proceeded on a “worst case” assumption that if ZnCdS were to degrade into its original sintered components, the most harmful product would be CdS. The report then focused upon the toxicological effects of CdS. It concluded that the amount of cadmium that people were exposed to in the trials were too low to pose a significant health risk.

A follow-up study by the US Army concluded that particulate ZnCdS remained intact in rats after pulmonary exposure and supported the NRC supposition that the compound was poorly bioavailable. ZnCdS was found to pass through the alveolar walls via macrophage action, but Zn and Cd were found present in the kidneys only in small amounts, were barely present in the liver, with no significant increase found in the blood. Proportionate (though slow, over 14 weeks) removal of Zn and Cd from the lungs indicated that the compound did not fragment; low liver and no significant blood levels of ZnCdS further argued against bioavailability. Some lung clearance was mucociliary in nature.

Some minor local and transitory toxic effects were noted: lung and lymph node inflammations, accumulations of foreign bodies in the lung, and altered enzyme, protein, and cell count levels. The experimental doses tested (on a body weight relative basis) far exceeded (at least by a factor of 500) the highest level of human exposure in previous US Army tests. No other health effects were reported.

Other literature and uses of ZnCdS indicates that it lodges in capillaries after administration into the bloodstream. This is perhaps a factor to consider if ZnCdS is capable of passing into the bloodstream through the alveolar epithelium or other means.

A review of cadmium toxicity as a “worst-case” scenario (rendered less likely in light of the finding of zinc cadmium sulfate's lack of degradation and lack of bioavailability in the rat) reveals concerns over cancer, particularly lung cancer, although the high level of human carcinogenic potential of conventionally assumed to be the case has lately been challenged. CdS, the main toxic component of ZnCdS, has been shown to be genotoxic and recent studies show clastogenesis.

Possible effects of acute exposure to cadmium include acute chemical pneumonitis or metal fume fever. There is typically no inflammatory response to cadmium sulfide (in contrast to observed effects of ZnCdS in the rat lung). Renal toxicity has been noted and long-term exposure to cadmium, even at low doses, damages kidney tubules and results in renal dysfunction.

No psychogenic effects of exposure to ZnCdS are reported. General reactions to perceived exposure to agents in biological and chemical warfare uses can be found in the supplement under this contract “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents.”

Secondary source literature is sparse and multiple CAS numbers and terminological variations complicate searching. The CAS number used by the NRC is used by NIOSH to identify a product called “Cadmium Sulfide, Solid Soln. With Zinc Sulfide Silver Chloride-Doped” while “Cadmium Zinc Sulfide” is identified as 12442-27-2. British documents prefer to render “sulfide” as “sulphide.”

No published specific handling instructions for ZnCdS were found.

II. BACKGROUND DATA

Identification & Physical Chemistry

Project SHAD Chemical Agent Name: FP (Fluorescent Particle)

Chemical Formula: CdSZn, ZnCdS

Chemical Structure: (None available for this sintered compound; see discussion of varied forms on p.34 of NRC 1997)

CAS#: 12442-27-2 (NIOSH 1980b)
68583-45-9 (NRC 1997)
11129-14-9 (NIOSH 1972)
8048-07-5 (Corrigenda 2002)

Abbreviations: ZnCdS (Bergmann 2000); ZCS (Academy of Medical Sciences (UK) 2001)

Alternate Names: cadmium zinc sulfide; cadmium zinc sulphide

Molecular Weight: (none found for zinc cadmium sulfide)

Density (conflicting values): 4.0 g/cm³ (NRC 1997)
1.06g/cm³ (Duke Scientific Corporation 2001)

Sintering Point: ~900°C (NRC 1997)

Boiling Point: (none found for zinc cadmium sulfide)

Melting Point: (none found for zinc cadmium sulfide)

Excitation wavelength: 3100-4000A (NRC 1997)

Zinc Cadmium Sulfide (ZnCdS) is an insoluble, crystalline, sintered combination of zinc sulfide and cadmium sulfide

Use & History

Zinc cadmium sulfide (ZnCdS) is highly fluorescent, glowing yellow-green under ultraviolet (black) light. Zinc cadmium sulfide is used to make yellow pigments (PY35) for paints and plastics. It is also used in making semiconductor nanocrystals (“quantum dots”), which are fluorophores used as detection markers (Han et al 2001).

Sizes of particles can range from 0.5 – 10 microns, which make the compound easily dispersible in air and fluids. One application as a biological reagent is as a good marker for identifying zones of infarction in myocardial tissue (Weinbrenner et al, 1998; Yue et al, 2001; Pain et al, 2000). It has also been used in ischemia studies to visualize the ischemia risk zone in myocardial tissues (Weinbrenner et al, 1998; Yue et al, 2001; Pain et al, 2000) Zinc cadmium sulfide has been suggested as a means for recording the temperature of skin for diagnostic purposes (NRC 1997).

The US Army and British military used ZnCdS as a traceable simulant for biological warfare agents in the examination of meteorological dispersion around cities in the 1950s and 1960s because it is easily dispersed, atmospherically stable, and economically efficient to use. It was also considered to be a non-toxic compound and therefore ideal. The US Army and contractors conducted 34 tests throughout North America. City populations were at risk of exposure to various amounts of the compound; these cities included Minneapolis, Corpus Christi, St. Louis, and Fort Wayne. (NRC 1997). The British tests tended to be over less inhabited areas (Elliott 2002; Academy of Sciences 2001). In Project SHAD as well, ZnCdS was also used as an aerosolized tracer for biological agent dispersion (Project 112 2003).

III. TOXICOLOGY OF ZINC CADMIUM SULFIDE

Overview: NRC Study & “Worst-Case Scenario”

There has been relatively little study of the toxicology specifically of zinc cadmium sulfide. The most comprehensive review was the National Research Council's (NRC) report in 1997 in response to the public concern over the Army's use of ZnCdS in American cities. (NRC 1997). That study concluded that there was insufficient evidence to find any significant toxicity for the compound, particularly at the likely exposure levels in the test areas. The report's key basis for its findings was that ZnCdS is essentially inert physiologically, a fact which arises from its insolubility which renders it unlikely to become bioavailable. Specifically, the report noted “[the] lack of solubility of ZnCdS particles [considered] together with the limited toxicity studies implies that...inhaled particles are not likely to be absorbed from the lung into blood for systemic distribution” (NRC 1997).

The slim possibility of the compound entering the body through the lung and being fragmented into bioavailable constituents was deemed a “worst-case scenario” by the NRC. In that scenario, cadmium (Cd), and more specifically the compound cadmium sulfide (CdS), could become liberated and act as a toxic presence in the body. That “worst-case” scenario, and the implications derived from scholarship and research updated since then, is developed in the next full section of this review.

Since the NRC report, there have been two major additional published reports on the toxicity specifically of ZnCdS. A British Ministry of Defence review prepared by the Academy of Medical Sciences (UK), last updated in 2001, has supported the NRC conclusions. Nevertheless, a follow-up study performed at the behest of the US Army to assess the issue of ZnCdS bioavailability suggests that the passing of particulate ZnCdS from the lung does indeed take place, though it presents no significant bioavailability. (Bergmann et al 2000).

Alveolar Penetration, Poor Bioavailability

The follow-up study to the NRC report employed rats exposed to intratracheally-administered ZnCdS. It found that ZnCdS could indeed be carried through the alveolar wall via the action of macrophages (Bergmann et al 2000). The ability of macrophages to carry other inert substances through the alveolar epithelium is well demonstrated (Kato et al 2003; Patrick et al 1992). Despite the penetration however, ZnCdS was found to be poorly bioavailable, showing no significant presence in the blood or liver (causing only about 1% increased presence in the latter) and little in the kidneys. The results are consistent with lymphoid passage and elimination. Additionally, much clearance of administered ZnCdS from the lung was also concluded to be mucociliary, rather than through the systemic route (Bergmann et al. 2000).

This finding of poor bioavailability was supported by the fact that the levels of zinc and cadmium removed from the lung remained proportional. This accorded with the NRC's supposition that the substance is not broken down into its components in the lung, and therefore the "worst-case" scenario of liberated elemental or compound cadmium becoming systemically active is demonstrably unlikely (Bergmann et al 2000).

ZnCdS Toxic Effects

In general, ZnCdS has been viewed as essentially non-toxic, although thorough and more recent study is lacking. The few older animal tests suggest extraordinarily high LD₅₀ (lethal dose 50% kill) levels (NRC 1991):

LD₅₀ (oral) – Dog = >3.5g/kg (no deaths reported)

LD₅₀ (oral) – Rat = >7.6 g/kg (no deaths reported)

Some doubt, however, as to the full usefulness of these tests from the 1960s has been raised because of the age of the study and species difference (NRC 1997; Academy of Medical Sciences 2001).

No epidemiological, clinical, or case evaluations among persons or areas exposed to ZnCdS concentration during dispersion testing of the past were found which showed deleterious health effects traceable to the compound (NRC 1997, Elliott 2002, Academy of Sciences 2001). Key British military personnel most directly involved in dissemination and regular close handling of ZnCdS particulates during aerial test distributions in the 1950s and 1960s were found not to have discernible effects traceable to exposure (Elliott 2002).

The US Army follow-up tests published in 2000 found that after ZnCdS exposure rats manifested local transitory inflammation of the pulmonary tract, accumulation of foreign material in the lungs and mediastinal lymph nodes, along with enzyme, protein, and cell count level abnormalities in bronchoalveolar lavage fluid (Bergmann et al 2000). Full but slow clearance of the compound from the lungs took place over a period of 14 weeks with substantial removal by absorption or mucociliary passage beginning about a full week after administration. (It was noted, however, that primate pulmonary clearance rates may be as much as 10 times slower than that of rodents.) The lowest tested dose on a relative body-weight basis was estimated to be about 500 times the highest dose to which those residents who had undergone the US Army's dispersion testing had been subjected (Bergmann et al 2000).

A possible result of exposure with conceivable health implications is suggested by the behavior of ZnCdS in capillaries. ZnCdS is known to become lodged in capillaries and remain there, which as noted earlier, has enabled it to be used as a diagnostic and pathologic tool to visualize risk zones of infarction by perfusing myocardial tissue. (Downey; no date; Weinbrenner et al, 1998; Yue et al, 2001; Pain et al, 2000). Thus, it is

conceivable that if inhaled ZnCdS particles can enter the circulatory system after lung deposition, they might accumulate in blood capillaries. (The Army follow-up found only minute traces of ZnCdS in the liver and none in the blood of rats, suggesting only a minimal possibility of air-blood transmission (Bergmann 2000). Nevertheless, there is the possibility of some transmission of that type, and recent study has confirmed that alveolar epithelial cells can phagocytize fine particles and transport them into blood capillaries (Kato et al 2003).) No studies or reports of health effects of capillary action of ZnCdS, or expressed concerns about it have been found, however.

IV. WORST-CASE SCENARIO: CADMIUM TOXICITY

Overview

A “worst-case” health effects scenario of ZnCdS exposure was considered by the NRC in its 1997 report. The “worst-case” assumed that ZnCdS might become bioavailable by breaking down into its components, which includes cadmium sulfide, and exposing the recipient of the administration to the toxicity of cadmium through circulatory transmission. This section updates the NRC review of the effects of inhaled cadmium as a possible worst-case scenario.

The reason for examining data specifically for the cadmium sulfide as the "worst-case" scenario was because the toxic effects of that ZnCdS component compound poses the highest risk to human health (NRC 1997).

As noted in the previous section, a subsequent study by the Army found that the fragmenting of the sintered compound ZnCdS did not appear to take place, presumably rendering the worst-case scenario still less likely. It also found that systemic availability through the blood after pulmonary exposure was minute. General bioavailability was concluded to be poor to the low presence of administered zinc and cadmium in the kidneys and liver (Bergmann 2000).

Inhaled cadmium’s pathophysiology has two noted characteristics. There is initial rapid clearance of the lung burden, followed by slower clearance of the rest (Klimisch 1993; Bergmann et al, 2000; NRC 1997). Cadmium accumulates in the kidneys and affects the skeletal system by interfering with calcium metabolism (Jarup et al 1998; Elliott et al 2000; Jakubowski 2001).

The NRC (1997) reports the following as the major toxicological considerations of cadmium and cadmium compound exposure:

- 1) The greatest risk from inhaled cadmium is to the lungs, causing lung cancer
- 2) Inhaled cadmium is most toxic to lungs, kidneys and the skeletal system

Carcinogenicity

In 1993, the International Agency IARC classified cadmium and cadmium compounds as a carcinogen of Group 1: *The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans* (IARC 1993b)

Within the past few years, however, conflicting reports have come out regarding cadmium’s carcinogenic effect in humans. There are epidemiological links of cadmium exposure with lung and prostate cancer in humans (Waalkes 2003; Waalkes 2000). Nevertheless, some more recent reports have asserted that there is insufficient evidence

for a carcinogenic effect in humans, and specifically recommend that cadmium not be assigned to IARC Group 1 (*carcinogenic to humans*) but rather to Group 2A (*probably carcinogenic to humans*) (Satoh et al 2002; Koyama et al, 2002).

Genotoxicity

The following presents recent data showing direct mutagenic effects of cadmium:

Peripheral lymphocytes from workers exposed to high cadmium concentrations were analyzed for DNA damage. The increase in DNA fragmentation and sister chromatid exchanges supports a clastogenic effect of cadmium. (Palus et al 2002)

Recent studies on cultured mammalian cells indicate that cadmium has a mutagenic effect by affecting DNA repair mechanisms (such as mismatch repair), as well as strand breaks, and chromosomal aberrations (Jin et al 2003; Hartwig and Schwertle 2002; Satoh et al 2002).

Acute Effects

Acute cadmium inhalation affects the lungs by causing either chemical pneumonitis or metal fume fever. Large concentrations can be fatal. (Ando et al 1996) There is typically no acute inflammatory lung response to cadmium sulfide. (NRC 1997; Bakshi & Henderson 1998) (This characteristic contrasts with the results of the Army follow-up study assessing acute exposure of zinc cadmium sulfide to rats, in which an acute inflammatory response was found. (Bergmann et al 2000))

Chronic Effects

Long-term exposure to cadmium, even at low doses, damages kidney tubules and results in renal dysfunction (Satoh et al 2002; Jarup et al 1998)

V. PSYCHOGENIC EFFECTS

It should be noted that people were very disturbed in both the US and UK upon learning of the dispersion testing (Bakshi and Henderson 1998; Academy of Medical Sciences 2001). To date, however, we have no published reports of clinical psychogenic presentations specifically relating to zinc cadmium sulfide exposure. A report on the psychogenic effects of perceived exposure to biological and chemical warfare testing can be found in the supplement under this contract, “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents”.

VI. TREATMENT & PREVENTION

There is no mention in the literature for treatment of zinc cadmium sulfide exposure or treatment for inert particulate inhalation. While there is no published literature on the methodology of handling zinc cadmium sulfide, follow-ups of the personnel who handled and dispersed the aerosol material in the British tests found no health effects attributable to the contact (Elliott et al 2002).

Cadmium and its compounds are subject to standard industrial safety measures for an occupational carcinogen (HSDB 2004).

VII. SECONDARY SOURCE COMMENT

Zinc cadmium sulfide in the Project 112 (SHAD) website states gives information consistent with the state of the literature (Project 112 2003):

....There has been little scientific study on the toxicity of this compound when inhaled. A National Research Council (NRC) committee focused on the cadmium component as potentially most toxic. While higher concentrations and more prolonged exposures to cadmium are associated with the development of lung cancer, the concentrations and durations of exposure in the Army's tests were substantially lower. The NRC committee concluded that the risk of adverse health effects to populations in the area was low.

A significant problem in research is the multiplicity of CAS numbers and designation names for ZnCdS. For example, the NRC lists 68583-45-9 as the Chemical Abstract Service (CAS) number for the compound zinc cadmium sulfide but the National Institute for Occupational Safety and Health (NIOSH) in a National Occupational Exposure Survey lists "Cadmium Sulfide, Solid Soln. With Zinc Sulfide Silver Chloride-Doped" as the agent name for the same CAS number (68583-45-9). The Survey also assigns a different CAS# 12441-27-2 for a compound named "Cadmium Zinc Sulfide" which appears to be zinc cadmium sulfide (NIOSH (1981-1983)a); NIOSH (1981-1983)b); NIOSH (1981-1983)c).

British reports tend to spell the name as "zinc cadmium sulphide" (Academy of Medical Sciences 2001, Elliott et al 2002). Variant names – cadmium zinc sulfide, etc. – along with the careless error of misstating the name of the agent as zinc cadmium *sulfate*, etc. can add considerable nuisance time to research on this compound (Emedco 1992a; Emedco 1992b; Downey no date).

VII.BIBLIOGRAPHY WITH ABSTRACTS

{The following bibliography includes supplemental material not cited in the text, in addition to the text citations. Unless otherwise noted, the abstracts for the following references are rendered verbatim as provided by the original publication or as made available in a standard print or electronic catalogue, or database. Errors, omissions, or other defects of language, form, style, or substance are strictly those of the original source or its transmission.}

Academy of Medical Sciences 2001. *Zinc Cadmium Sulphide Dispersion Trials. Report by the Academy of Medical Sciences to the Chief Scientific Adviser, Ministry of Defence on the Zinc Cadmium Sulphide dispersion trials undertaken in the United Kingdom between 1953 and 1964.* Ministry of Defence (Last update Sept. 3, 2001) [available at http://www.mod.uk/publications/zinc_cadmium/index.htm].

Ando, et al. 1996. Elevated urinary cadmium concentrations in a patient with acute cadmium pneumonitis. *Scand.J.Work Environ.Health.* Vol. 22(2): 150-153.
BACKGROUND: Acute serious inhalation of cadmium fumes often causes chemical pneumonitis or metal fume fever. Because symptoms of both diseases begin several hours after exposure and closely mimic each other, one often mistakes chemical pneumonitis for metal fume fever in the early stages. It is, however, essential to differentiate between the two since chemical pneumonitis can progress to serious consequences. CASE: A 43-year-old man was admitted to the hospital 2 d after exposure to cadmium fumes. The initial diagnosis was metal fume fever on the basis of his history, and he was treated accordingly. His symptoms worsened however, and transient renal impairment was identified as consistent with cadmium-induced renal toxicity. Although the possibility of drug-induced renal damage could not be excluded, abnormal urinalysis findings on admission suggested that the renal tubular damage was caused by inhaled cadmium before admission. CONCLUSIONS: Measuring the urinary cadmium concentration is an effective method for confirming acute cadmium poisoning.

Ato, et al. 1981. Development of scintillators for alpha- and beta-rays –comparison of relative luminescence of scintillation and photoluminescence of various phosphors (author's transl). *Radioisotopes.* Vol. 30(2): 73-79.
Relative scintillation efficiencies of various phosphors such as ZnS, ZnCdS and Zn₂SiO₄ under excitation by alpha-rays from ²¹⁰Po, beta-rays from ⁹⁰Sr-⁹⁰Y were compared with those excited by 365 nm (3650A) UV light. The influence on the structure, mixture rate, firing atmosphere and firing temperature of phosphors on the efficiency were noted. The results were as follows: (1) ZnS type phosphors generally showed the highest

efficiencies under all types of excitation examined. (2) Among ZnS: Cu type phosphors, the specimen fired at 1100 degree C was the most efficient under the three types of excitation. (3) A highly efficient phosphor in photoluminescence was not always efficient in scintillation. (4) The addition of a flux was generally effective for scintillation as for photoluminescence. (5) The phosphors fired in H₂S showed a lower efficiency than those fired in air on N₂ in both scintillation and photoluminescence.

Bakshi and Henderson 1998. Toxicologic Assessment of the Army's Zinc Cadmium Sulfide Dispersion Tests. *Inhal. Toxicol.* Vol. 10: 895-904

Bergmann, et al. 2000. Intratracheal instillation of zinc-cadmium sulfide (ZnCdS) in Fischer 344 rats. *Inhal. Toxicol.* Vol. 12(4): 331-346.

The purpose of this study was to assess the bioavailability and pulmonary toxicity of ZnCdS in rats. Groups of 30 male Fischer 344 rats each were anesthetized and dosed via intratracheal instillation with 5 mg of either ZnCdS, quartz (positive control), or titanium dioxide (TiO₂), negative control) suspended in 0.5 ml saline. A vehicle control group received 0.5 ml saline. Ten animals from each test group were sacrificed at 1 day, 1 wk, and 14 wk after dosing for bronchoalveolar lavage fluid (BALF) analysis and histopathology. The BALF was analyzed for alkaline phosphatase, acid phosphatase, lactate dehydrogenase (LDH), beta-glucuronidase (beta-glu), total protein, and cell counts. Two separate groups of 24 rats each were dosed as already described with either ZnCdS or saline. Eight rats from each group were sacrificed at 1 day, 1 wk, and 14 wk after dosing for determination of cadmium (Cd) and zinc (Zn) concentrations in the lung, liver, kidney, and blood. Results indicate that at 1 day after dosing, all enzyme activities (except acid phosphatase) and cell counts in BALF from the quartz and ZnCdS groups were significantly higher than in the TiO₂ and saline groups. At 7 days after dosing, high enzyme activity persisted in the quartz group, while the ZnCdS group showed only LDH and total protein levels significantly higher than the saline group. At 14 wk after dosing, LDH, total protein, beta-glu, and cell counts in the quartz group were significantly higher than all other groups. Histologic examination revealed interstitial inflammation and accumulation of foreign material in the lungs and mediastinal lymph nodes of quartz-, TiO₂-, and ZnCdS-treated rats. Metal analyses in tissues showed profuse Cd and Zn concentrations in the lung 1 day after dosing, followed by a successive decline at 7 days and 14 wk after dosing. A very small, but statistically significant, amount of Cd and Zn was found in the kidneys at 14 wk after dosing. In conclusion, ZnCdS appears to cause temporary lung inflammation, is cleared slowly, and is poorly bioavailable.

Corrigenda 2002. *Official Journal of the European Communities* C 146 A of 15 June 1990 (2002/C 54/08). [http://europa.eu.int/eur-lex/pri/en/oj/dat/2002/c_054/c_05420020301en00130037.pdf; http://europa.eu.int/eurlex/en/archive/2002/c_05420020301en.html]

Downey, no date. Measuring infarct size by the tetrazolium method.
[<http://www.southalabama.edu/ishr/help/ttc/>]

Duke Scientific Corporation 2001. *Technical Note-009A: Use of Fluorescent Polymer Microspheres for Marking the Risk Zone in Myocardial Infarct Studies.* [<http://www.dukescientific.com/pdfs/tech/tn00901Web.pdf>]

Elliott, et al. 2000. Risk of mortality, cancer incidence, and stroke in a population potentially exposed to cadmium. *Occup. Environ. Med.* Vol. 57(2): 94-97.
OBJECTIVES: To follow up mortality and cancer incidence in a cohort potentially exposed to cadmium and to perform a geographical (ecological) analysis to further assess the health effects of potential exposure to cadmium. METHODS: The English village of Shipham has very high concentrations of cadmium in the soil. A previous cohort study of residents of Shipham in 1939 showed overall mortality below that expected, but a 40% excess of mortality from stroke. This study extends the follow up of the cohort for mortality to 1997, and includes an analysis of cancer incidence from 1971 to 1992, and a geographical study of mortality and cancer incidence. Standardised mortality and incidence ratios (SMRs and SIRs) were estimated with regional reference rates. Comparisons were made with the nearby village of Hutton. RESULTS: All cause cohort mortality was lower than expected in both villages, although there was excess cancer incidence in both Shipham (SIR 167, 95% confidence interval (95% CI) 106 to 250) and Hutton (SIR 167, 95% CI 105 to 253). There was an excess of mortality from hypertension, cerebrovascular disease, and nephritis and nephrosis, of borderline significance, in Shipham (SMR 128, 95% CI 99 to 162). In the geographical study, all cause mortality in Shipham was also lower than expected (SMR 84, 95% CI 71 to 100). There was an excess in genitourinary cancers in both Shipham (SIR 160, 95% CI 107 to 239) and Hutton (SIR 153, 95% CI 122 to 192). CONCLUSION: No clear evidence of health effects from possible exposure to cadmium in Shipham was found despite the extremely high concentrations of cadmium in the soil.

Elliott, et al. 2002. The risk to the United Kingdom population of zinc cadmium sulfide dispersion by the Ministry of Defence during the "cold war" *Occup. Environ. Med.* Vol. 59(1): 13-17.
OBJECTIVES: To estimate exposures to cadmium (Cd) received by the United Kingdom population as a result of the dispersion of zinc Cd sulfide (ZnCdS) by the Ministry of Defence between 1953 and 1964, as a simulator of biological warfare agents. METHODS: A retrospective risk assessment study was carried out on the United Kingdom population during the period 1953-64. This determined land and air dispersion of ZnCdS over most of the United Kingdom, inhalation exposure of the United Kingdom population, soil contamination, and risks to personnel operating equipment that dispersed ZnCdS. RESULTS: About 4600 kg ZnCdS were dispersed from aircraft and ships, at times when the prevailing winds would allow large areas of the country to be covered. Cadmium released from 44 long range trials for which data are available, and extrapolated to a total of 76 trials to allow for trials with incomplete information, is about

1.2% of the estimated total release of Cd into the atmosphere over the same period. “Worst case” estimates are 10 microg Cd inhaled over 8 years, equivalent to Cd inhaled in an urban environment in 12100 days, or from smoking 100 cigarettes. A further 250 kg ZnCdS was dispersed from the land based sites, but significant soil contamination occurred only in limited areas, which were and have remained uninhabited. Of the four personnel involved in the dispersion procedures (who were probably exposed to much higher concentrations of Cd than people on the ground), none are suspected of having related illnesses. CONCLUSION: Exposure to Cd from dissemination of ZnCdS during the “cold war” should not have resulted in adverse health effects in the United Kingdom population.

Emedco 1992a UN2030 Omnicolor Pale Orange MSDS bpjrx

url: http://www.emedco.com/emed2/resource/msds/msds_view.asp?pd=ba&pf=bpjrx

Emedco 1992b UN6908 Omnicolor Military Green MSDS bpgwf

url: http://www.emedco.com/emed2/resource/msds/msds_view.asp?pd=ba&pf=bpgwf

Haessler, et al. 1994. Anaesthetics alter the magnitude of infarct limitation by ischaemic preconditioning. *Cardiovasc.Res.* Vol. 28(10): 1574-1580.

OBJECTIVE: The aim was to determine whether three commonly used animal anaesthetics alter the magnitude of infarct limitation achieved with ischaemic preconditioning. METHODS: Eighty four □ransferring□ non-preconditioned and preconditioned open chest rabbits underwent a 30 min coronary occlusion followed by 3 h reperfusion. Ischaemic preconditioning was achieved with 5 min coronary occlusion beginning 15 min before the 30 min coronary occlusion. The anaesthetics studied were: pentobarbitone (30 mg.kg-1 intravenously +30-50 mg.kg-1.h-1 intravenously), isoflurane (1.5-2.5% end expiratory), and ketamine/xylazine (cocktail of 67 mg ketamine and 6.7 mg xylazine.ml-1, 1 ml.kg-1 intramuscularly +0.3-1.3 ml.kg-1.h-1 intramuscularly). Area at risk was delineated with ZnCdS particles and infarction assessed with tetrazolium. RESULTS: There were no significant differences in area at risk, heart rate, arterial pressure, and temperature between non-preconditioned and preconditioned hearts. Although infarct size was not significantly different among non-preconditioned hearts for each anaesthetic regimen (p = NS), the magnitude of infarct limitation with preconditioning varied with the anaesthetic employed (decrease in infarct size from control values of 81%, 44%, and 33% for pentobarbitone, isoflurane and ketamine/xylazine, respectively, p = 0.0145 for comparison of the three magnitudes, two factor ANOVA). CONCLUSION: Anaesthetic regimens affect the degree of infarct size limitation seen with ischaemic preconditioning.

Han, et al. 2001. Quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules. *Nat.Biotechnol.* Vol. 19(7): 631-635.

Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots (zinc sulfide-capped cadmium selenide nanocrystals) into polymeric microbeads at precisely controlled ratios. Their novel optical properties (e.g., size-tunable emission and simultaneous excitation) render these highly luminescent quantum dots (QDs) ideal fluorophores for wavelength-and-intensity multiplexing. The

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use of 10 intensity levels and 6 colors could theoretically code one million nucleic acid or protein sequences. Imaging and spectroscopic measurements indicate that the QD-tagged beads are highly uniform and reproducible, yielding bead identification accuracies as high as 99.99% under favorable conditions. DNA hybridization studies demonstrate that the coding and target signals can be simultaneously read at the single-bead level. This spectral coding technology is expected to open new opportunities in gene expression studies, high-throughput screening, and medical diagnostics.

Hartwig, et al. 2002. Interactions by carcinogenic metal compounds with DNA repair processes: toxicological implications. *Toxicol.Lett.* Vol. 127(1-3): 47-54. Even though compounds of nickel, arsenic, cobalt and cadmium are carcinogenic, their mutagenic potentials are rather weak. In contrast, they exert pronounced comutagenic effects, which may be explained by disturbances of different DNA repair systems. Thus, cobalt, arsenic, nickel and cadmium interfere with base and nucleotide excision repair, even though they affect different steps of the respective repair systems and act by different, not yet completely understood mechanisms. Potential target molecules for some metal ions are so-called zinc finger structures in DNA repair proteins, but each zinc finger protein exerts its own sensitivity towards toxic metal ions. Possible consequences of repair inhibitions are discussed in more detail for soluble and particulate nickel compounds, which have recently been shown to interfere with the repair of stable DNA adducts induced by benzo[a]pyrene (B[a]P). Since nickel compounds and polycyclic aromatic hydrocarbons such as B[a]P are frequently associated in the ambient air, in cigarette smoke and at many workplaces, an impaired removal of B[a]P-derived DNA adducts will lead to persistent DNA damage and thus increase the risk of mutations and tumor formation.

HSDB 2004. Cadmium Compounds. *Hazardous Substance Data Bank [An NLM-TOXNET Database]* [<http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~uNBE10:2>]

IARC (International Agency for Research on Cancer). 1993a. Cadmium and Cadmium Compounds (Group 1). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 58. [<http://www.inchem.org/documents/iarc/vol58/mono58-2.html>].

IARC (International Agency for Research on Cancer). 1993b. Evaluation. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol. 58 [<http://monographs.iarc.fr/monoeval/eval.html>]

Jakubowski 2001. Zinc and Cadmium. In Bingham et al eds. *Patty's Toxicology, 5th edition*. Vol. 2. (John Wiley & Sons, Inc.)

Jarup, et al. 1998. Health effects of cadmium exposure—a review of the literature and a risk estimate. *Scand.J.Work Environ.Health.* Vol. 24 Suppl 11-51.

This report provides a review of the cadmium exposure situation in Sweden and updates

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the information on health risk assessment according to recent studies on the health effects of cadmium. The report focuses on the health effects of low cadmium doses and the identification of high-risk groups. The diet is the main source of cadmium exposure in the Swedish nonsmoking general population. The average daily dietary intake is about 15 micrograms/day, but there are great individual variations due to differences in energy intake and dietary habits. It has been shown that a high fiber diet and a diet rich in shellfish increase the dietary cadmium intake substantially. Cadmium concentrations in agricultural soil and wheat have increased continuously during the last century. At present, soil cadmium concentrations increase by about 0.2% per year. Cadmium accumulates in the kidneys. Human kidney concentrations of cadmium have increased several fold during the last century. Cadmium in pig kidney has been shown to have increased by about 2% per year from 1984-1992. There is no tendency towards decreasing cadmium exposure among the general nonsmoking population. The absorption of cadmium in the lungs is 10-50%, while the absorption in the gastrointestinal tract is only a few percent. Smokers have about 4-5 times higher blood cadmium concentrations (about 1.5 micrograms/l), and twice as high kidney cortex cadmium concentrations (about 20-30 micrograms/g wet weight) as nonsmokers. Similarly, the blood cadmium concentrations are substantially elevated in persons with low body iron stores, indicating increased gastrointestinal absorption. About 10-40% of Swedish women of child-bearing age are reported to have empty iron stores (S-ferritin < 12 micrograms/l). In general, women have higher concentrations of cadmium in blood, urine, and kidney than men. The population groups at highest risk are probably smokers, women with low body iron stores, and people habitually eating a diet rich in cadmium. According to current knowledge, renal tubular damage is probably the critical health effect of cadmium exposure, both in the general population and in occupationally exposed workers. Tubular damage may develop at much lower levels than previously estimated, as shown in this report. Data from several recent reports from different countries indicate that an average urinary cadmium excretion of 2.5 micrograms/g creatinine is related to an excess prevalence of renal tubular damage of 4%. An average urinary excretion of 2.5 micrograms/g creatinine corresponds to an average concentration of cadmium in renal cortex of 50 micrograms/g, which would be the result of long-term (decades) intake of 50 micrograms per day. When the critical concentrations for adverse effects due to cadmium accumulation are being evaluated, it is crucial to consider both the individual variation in kidney cadmium concentrations and the variations in sensitivity within the general population. Even if the population average kidney concentration is relatively low for the general population, a certain proportion will have values exceeding the concentration where renal tubular damage can occur. It can be estimated that, at the present average daily intake of cadmium in Sweden, about 1% of women with low body iron stores and smokers may experience adverse renal effects related to cadmium. If the average daily intake of cadmium would increase to 30 micrograms/day, about 1% of the entire population would have cadmium-induced tubular damage. In risk groups, for example, women with low iron stores, the percentage would be higher, up to 5%. Both human and animal studies indicate that skeletal damage (osteoporosis) may be a critical effect of cadmium exposure. We conclude, however, that the present evidence is not sufficient to

permit such a conclusion for humans. We would like to stress, however, that osteoporosis is a very important public health problem worldwide, but especially in the Scandinav

Jin, et al. 2003. Cadmium is a mutagen that acts by inhibiting mismatch repair. *Nat. Genet.* Vol. 34(3): 326-329.

Most errors that arise during DNA replication can be corrected by DNA polymerase proofreading or by post-replication mismatch repair (MMR). Inactivation of both mutation-avoidance systems results in extremely high mutability that can lead to error catastrophe. High mutability and the likelihood of cancer can be caused by mutations and epigenetic changes that reduce MMR. Hypermutable can also be caused by external factors that directly inhibit MMR. Identifying such factors has important implications for understanding the role of the environment in genome stability. We found that chronic exposure of yeast to environmentally relevant concentrations of cadmium, a known human carcinogen, can result in extreme hypermutability. The mutation specificity along with responses in proofreading-deficient and MMR-deficient mutants indicate that cadmium reduces the capacity for MMR of small misalignments and base-base mismatches. In extracts of human cells, cadmium inhibited at least one step leading to mismatch removal. Together, our data show that a high level of genetic instability can result from environmental impediment of a mutation-avoidance system.

Kaji, et al. 2002. [Low dose exposure to cadmium and its health effects (2). Life-cycle related diseases and reproductive toxicity]. *Nippon Eiseigaku Zasshi.* Vol. 57(3): 556-563.

We have reviewed earlier studies on the possible involvement of cadmium in life-cycle related diseases and the reproductive toxicity of Cd including environmental disrupting actions. Experimental studies have suggested that Cd may be involved in the aggravation of life-cycle related diseases and the occurrence of reproductive toxicity. On the other hand, epidemiological studies did not necessarily support the experimental observations. Thus, we conclude that it is necessary to investigate further to determine whether Cd is responsible for the aggravation of life-cycle related diseases or has the capability to act as an environmental endocrine disrupter in humans.

Kato, et al. 2003. Evidence that exogenous substances can be phagocytized by alveolar epithelial cells and transported into blood capillaries. *Cell Tissue Res.* Vol. 311(1): 47-51.

Since the ability of alveolar epithelial cells to ingest inhaled fine particles has not been characterized in detail, the present study seeks to evaluate this physiological activity. We used a 0.2% suspension of intact or lecithin-coated polystyrene latex beads (240 nm in diameter). A 5-ml suspension of intact or lecithin-coated latex beads was intratracheally administered to rats using a compressor nebulizer. Thereafter, the lungs were perfused intratracheally with glutaraldehyde solution and cut into small pieces. The samples were postfixed with osmium tetroxide, embedded in epoxy resin and examined under an electron microscope. Both lecithin-coated and uncoated beads were incorporated into alveolar macrophages. Some of the ingested beads in the alveolar macrophages were sequestered within lysosomes. Types I and II alveolar epithelial cells selectively

incorporated only lecithin-coated beads, which were also observed within the cytoplasm of monocytes in the capillary lumen. These findings suggest that alveolar epithelial cells can incorporate exogenous particles, which are then transferred from the alveoli to intravascular spaces by transcytosis.

Klimisch. 1993. Lung deposition, lung clearance and renal accumulation of inhaled cadmium chloride and cadmium sulphide in rats. *Toxicology*. Vol. 84(1-3): 103-124. Rats were exposed 6 h/day over 10 days to 0.3 mg/m³ of water soluble cadmium chloride and 0.2, 1.0 and 8.0 mg/m³ of insoluble cadmium sulphide, then killed at intervals over a 3-month period for serial measurements of lung, renal and faecal cadmium. CdCl₂ and high-dose CdS animals showed a transient increase in lung weight. Clearance of both compounds was biphasic. Approximately 40% of deposited material was cleared during the 10-day exposure period. For CdCl₂, only 9% of the lung burden was cleared rapidly after the last exposure (half-life 1.0 days) and 47% slowly (half-life 87 days), leaving a residual lung burden of 44%. For CdS, 41% of the lung burden was cleared rapidly (half-life 1.4 days) and 40% slowly (half-life 42 days), leaving a final residue 19%. In the CdS high-dose group, the retention of CdS in the lung was greater than that in the CdS low-dose groups, indicating that clearance mechanisms may possibly have been impaired in the high-dose group by too great a lung burden. For both compounds, faecal cadmium was initially high. Renal accumulation of cadmium was substantial for CdCl₂ during the exposure period and continued over the following months until it represented approximately 35% of the total cadmium cleared from the lung. For CdS, renal accumulation was only 1% of the amount cleared from the lung. The bioavailability of Cd from CdS is thus poor, the majority being cleared from the lungs and excreted in the faeces. However, the bioavailability of inhaled CdS measured as cadmium in the kidney is greater than the bioavailability of orally ingested CdS.

Koyama, et al. 2002. [Low dose exposure to cadmium and its health effects (1). Genotoxicity and carcinogenicity]. *Nippon Eiseigaku Zasshi*. Vol. 57(3): 547-555. We reviewed studies on genotoxicity and carcinogenicity of cadmium (Cd). Salmonella typhimurium and Escherichia coli exposed to Cd did not show mutagenicity, whereas cultured mammalian cells exposed to Cd showed mutation, DNA strand breaks, and chromosomal aberrations. Carcinogenicity tests showed that exposure to Cd increased the occurrence of tumors in testis, lung, prostate, hematopoietic tissues, and injection sites. On the other hand, recent epidemiologic studies are not supportive of earlier observations on the association between Cd and prostate cancer. The US NIOSH data on a possible association between Cd and lung cancer may need reevaluation. No studies which show a positive relationship between oral Cd exposure and carcinogenesis have been reported. All available data suggest that Cd should be reassigned to IARC Group 2A (probably carcinogenic to humans) from the current Group 1.

LAWSON, et al. 1965. SKIN TEMPERATURE RECORDING WITH PHOSPHORS: A NEW TECHNIQUE. *Can.Med.Assoc.J.* Vol. 92:255-260.

Lay, et al. 2001. Effects of inhaled iron oxide particles on alveolar epithelial permeability in normal subjects. *Inhal.Toxicol.* Vol. 13(12): 1065-1078.

Pulmonary inflammation secondary to oxidant generation catalyzed by transition metals associated with inhaled particles is one factor postulated to underlie the acute health effects of particulate air pollution. We postulated that inhaled iron oxide particles with associated amounts of soluble iron should induce mild pulmonary inflammation and lead to altered alveolar epithelial integrity and altered gas exchange. To test this hypothesis we examined the effects of inhaled iron oxide particles on alveolar epithelial permeability. Sixteen healthy subjects inhaled aerosols of iron oxide particles (1.5 microm mass median aerodynamic diameter) having either high or low water-soluble iron content [3.26 +/- 0.25 (SE) and 0.14 +/- 0.04 microg soluble iron/mg of particles, respectively] for 30 min at an average mass concentration of 12.7 mg/m³. Alveolar epithelial permeability was assessed by measuring the pulmonary clearance of an inhaled radiolabeled tracer molecule ((99m)Tc-DTPA, diethylene triamine pentaacetic acid) using a gamma camera at 1/2 h and 24 h post particle exposure. Carbon monoxide lung diffusing capacity (DL(CO)) and spirometry were also performed before and after breathing the iron oxide. As a control, on a separate day, the procedures were duplicated except that the subject breathed particle-free air. For those subjects breathing aerosols with high soluble iron, we found no significant difference in DTPA clearance half-times after breathing particles versus particle-free air either at 1/2 h (97.4 +/- 15.4 vs. 116.1 +/- 15.5 min, respectively) or 24 h postinhalation (105.1 +/- 13.8 vs. 106.9 +/- 12.9 min, respectively). Likewise, for those subjects breathing aerosols with low soluble iron content we found no significant difference in DTPA clearance half-times after breathing particles versus particle-free air either at 1/2 h (108.6 +/- 31.9 vs. 95.6 +/- 10.8 min, respectively) or 24 h postinhalation (130.0 +/- 18.0 vs. 105.8 +/- 13.7 min, respectively). We found no significant differences in DL(CO) between particle exposures and air exposures. Minor differences in spirometric measurements were noted but were not statistically significant. We conclude that inhalation of iron oxide particles did not cause an appreciable alteration of alveolar epithelial permeability, lung diffusing capacity, or pulmonary function in healthy subjects under the studied conditions.

Lindstrom, et al. 1999. A simple model for estimating the particle size dependence of absolute efficiency of fluorescent screens. *Phys.Med.Biol.* Vol. 44(5): 1353-1367.

The absolute efficiency of a phosphor screen is the ratio of the light energy per unit area at the screen surface to the incident x-ray energy fluence. Particle size is a critical factor in determining the absolute efficiency, but in most models its influence is not accounted for. To allow derivation of the particle size dependence, a model is proposed that describes the optical properties of the screen by means of a single parameter, the light extinction factor, ξ , and assumes that the intrinsic efficiency (light energy/energy imparted to the phosphor material) is independent of particle size. The value of ξ depends on the type of screen (phosphor, reflective backing, coating and binder) and has to be determined from measurements on at least two screens with known particle size and thickness. The absolute efficiency can then be calculated for an extended range of particle sizes and/or screen thicknesses. To test the model, experimental data from the literature were used to derive values of ξ for screens of La₂O₂S:Tb, LaOBr:Tm and ZnCdS:Ag.

The extinction factor was found to vary between -6 and +20%. The non-physical negative value for ξ , found from one set of experiments on La₂O₂S:Tb screens, may be explained as resulting from a lack of accurate knowledge of the actual tube potential, influencing calculated values of the energy imparted to the screen. The results are promising but further well-controlled experiments (including improved dosimetric calculations to account for foreshortening of K-radiation from the screen) are needed to confirm the model.

Mainprize, et al. 1998. The effect of phosphor persistence on image quality in digital x-ray scanning systems. *Med.Phys.* Vol. 25(12): 2440-2454.

A digital x-ray scanning system offers several advantages over conventional film-screen systems. However, there are sources of image degradation resulting from the scanning motion, such as motion blur due to the temporal response of the phosphor. This mechanism produces an asymmetrical blur, requiring the use of the complex optical transfer function (OTF) rather than the normal modulation transfer function (MTF) for correct characterization of image resolution. The luminescence response of eight phosphors was measured under pulsed x-ray excitation. A weighted exponential model was used to represent the primary luminescence. The dominant luminescence life-times ranged from 2.7 microseconds for Gd₂O₂S:Pr to 558 microseconds for Gd₂O₂S:Tb. The long term response was also measured, monitoring significant increases in a slow form of luminescence known as afterglow. Afterglow was modeled by an inverse power law equation. Afterglow was found to be strong in two of the phosphors studied (ZnCdS:Ag and Y₂O₃:Tb). In selecting a phosphor for a scanning system, it must satisfy several criteria, including a fast temporal response. Thus, a phosphor like Gd₂O₂S:Tb, which has a slow luminescence, but otherwise excellent imaging properties, may not be as useful as a more rapid phosphor like CsI:Tl.

Muller, et al. 1989. Cellular aspects of retention and transport of inhaled soluble and insoluble actinide compounds in the rat lung. *Sci.Total Environ.* Vol. 83(3): 239-251. The binding of ²⁴¹Am-hydroxide polymers (as models for readily soluble actinide compounds) to the cell components of rat lung was investigated using differential centrifugation, density gradient centrifugation, gel chromatography, carrier-free electrophoresis and electron microscopic autoradiography (with ²⁴¹Pu). Irregularly shaped and spherical mixed (U, Pu)O₂ particles (as models for insoluble actinide compounds) were administered to rats by inhalation and intratracheal installation and the lung and organ retention was determined. Electron microscopic studies were performed with rat lung and with rat and bovine alveolar macrophages exposed to the actinide compounds in vitro. In the case of the mixed (U, Pu)O₂ particles the lung retention was independent of the particle shape and route of administration. Whereas ²⁴¹Am administered as a hydroxide polymer was transferred rapidly from lung to skeleton and liver, only a few percent of the initial alveolar deposit was found in these organs after mixed oxide inhalation. It is concluded that all types of particles are stored primarily within phagolysosomes of alveolar macrophages. In the case of readily soluble compounds, the actinides are solubilized within these lysosomes and become bound to cytosolic ferritin in the alveolar macrophages. They are then released from the

macrophages and probably cross the alveolar membranes as □ransferring or as low-molecular-weight forms. Insoluble compounds remain within the lysosomes of alveolar macrophages, but there are indications of chemical damage to the lysosomal membranes, causing the particles to lie free in the cytoplasm.

NIOSH 1983a. *National Occupational Exposure Survey (1981-1983)a. Estimated Numbers of Employees Potentially Exposed to Specific Agents by Occupation within 2-Digit Standard Industrial Classification (SIC)* CADMIUM SULFIDE, SOLID SOLN. WITH ZINC SULFIDE, SILVER CHLORIDE-DOPED.* [<http://www.cdc.gov/noes/noes4/x1319sco.html>].

NIOSH 1983b. *National Occupational Exposure Survey (1981-1983)b. Estimated Numbers of Employees Potentially Exposed to Specific Agents by Occupation CADMIUM ZINC SULFIDE (CDZNS).* [<http://www.cdc.gov/noes/noes2/e0564occ.html>].

NIOSH 1983c. *National Occupational Exposure Survey (1981 – 1983)c. Estimated Numbers of Employees Potentially Exposed to Specific Agents by 2-Digit Standard Industrial Classification (SIC)* CADMIUM ZINC SULFIDE.* [<http://www.cdc.gov/noes/noes1/x4133sic.html>]

NRC (National Research Council) 1997. *Toxicologic Assessment of the Army's Zinc Cadmium Sulfide Dispersion Tests.* (National Academy Press).

Pain, et al. 2000. Opening of mitochondrial K(ATP) channels triggers the preconditioned state by generating free radicals. *Circ.Res.* Vol. 87(6): 460-466.

The critical time for opening mitochondrial (mito) K(ATP) channels, putative end effectors of ischemic preconditioning (PC), was examined. In isolated rabbit hearts 29±3% of risk zone infarcted after 30 minutes of regional ischemia. Ischemic PC or 5-minute exposure to 10 micromol/L diazoxide, a mito K(ATP) channel opener, reduced infarction to 3±1% and 8±1%, respectively. The mito K(ATP) channel closer 5-hydroxydecanoate (200 micromol/L), bracketing either 5-minute PC ischemia or diazoxide infusion, blocked protection (24±3 and 28±6% infarction, respectively). However, 5-hydroxydecanoate starting 5 minutes before long ischemia did not affect protection. Glibenclamide (5 micromol/L), another K(ATP) channel closer, blocked the protection by PC only when administered early. These data suggest that K(ATP) channel opening triggers protection but is not the final step. Five minutes of diazoxide followed by a 30-minute washout still reduced infarct size (8±3%), implying memory as seen with other PC triggers. The protection by diazoxide was not blocked by 5 micromol/L chelerythrine, a protein kinase C antagonist, given either to bracket diazoxide infusion or just before the index ischemia. Bracketing preischemic exposure to diazoxide with 50 micromol/L genistein, a tyrosine kinase antagonist, did not affect infarction, but genistein blocked the protection by diazoxide when administered shortly before the index ischemia. Thus, although it is not protein kinase C-dependent, the protection by diazoxide involves

tyrosine kinase. Bracketing diazoxide perfusion with N:-(2-mercaptopropionyl) glycine (300 micromol/L) or Mn(III)tetrakis(4-benzoic acid) porphyrin chloride (7 micromol/L), each of which is a free radical scavenger, blocked protection, indicating that diazoxide triggers protection through free radicals. Therefore, mito K(ATP) channels are not the end effectors of protection, but rather their opening before ischemia generates free radicals that trigger entrance into a preconditioned state and activation of kinases.

Palus, et al. 2003. Genotoxic effects of occupational exposure to lead and cadmium. *Mutat.Res.* Vol. 540(1): 19-28.

This study was designed to assess genotoxic damage in somatic cells of workers in a Polish battery plant after high-level occupational exposure to lead (Pb) and cadmium (Cd), by use of the following techniques: the micronucleus (MN) assay, combined with in situ fluorescence hybridization (FISH) with pan-centromeric probes, analysis of sister chromatid exchanges (SCEs), and the comet assay. Blood samples from 44 workers exposed to lead, 22 exposed to cadmium, and 52 unexposed persons were used for SCE and MN analysis with 5'-bromodeoxyuridine (BrdU) or cytokinesis block, respectively. In parallel, the comet assay was performed with blood samples from the same persons for detection of DNA damage, including single-strand breaks (SSB) and alkali-labile sites (ALS). In workers exposed mostly to lead, blood Pb concentrations ranged from 282 to 655 microg/l, while the range in the controls was from 17 to 180 microg/l. Cd concentration in lead-exposed workers fell in the same range as for the controls. In workers exposed mainly to cadmium, blood Cd levels varied from 5.4 to 30.8 microg/l, with respective values for controls within the range of 0.2-5.7 microg/l. Pb concentrations were similar as for the controls. The incidence of MN in peripheral lymphocytes from workers exposed to Pb and Cd was over twice as high as in the controls ($P < 0.01$). Using a combination of conventional scoring of MN and FISH with pan-centromeric probes, we assessed that this increase may have been due to clastogenic as well as aneugenic effects. In Cd- and Pb-exposed workers, the frequency of SCEs as well as the incidence of leukocytes with DNA fragmentation in lymphocytes were slightly, but significantly increased ($P < 0.05$) as compared with controls. After a 3h incubation of the cells to allow for DNA repair, a clear decrease was found in the level of DNA damage in the controls as well as in the exposed workers. No significant influence of smoking on genotoxic damage could be detected in metal-exposed cohorts. Our findings indicate that lead and cadmium induce clastogenic as well as aneugenic effects in peripheral lymphocytes, indicating a potential health risk for working populations with significant exposures to these heavy metals.

Patrick, et al. 1992. Transport of particles of colloidal gold within and from rat lung after local deposition by alveolar microinjection. *Environ.Health Perspect.* Vol. 97:47-51.

Because inhalation and intratracheal instillation deposit particles throughout the respiratory tract, these methods of administration give little information on the movement of particles within the lung and no direct information on the clearance kinetics from locally defined sites within alveolar tissue. Approximately 0.05 microL of ^{195}Au -labeled gold colloid was administered to 32 rats by microinjection into a small volume of

subpleural alveoli. Its fate was studied by whole-body counting and serial sacrifice over 15 months. The kinetics of clearance from the subpleural deposition site showed that there was no rapid removal of particles, and the main clearance process was defined by an exponential term with a half-time averaging 583 days. There was a wide variation between individual animals. The distribution of ^{195}Au at sacrifice showed that the gold colloid was nearly all retained within the respiratory tract. The particles were not appreciably redistributed throughout the lung volume, so most of the material not cleared from the lung remained close to the deposition site. At the later times after microinjection, much of the gold colloid was associated with thickened pleura and adjoining septae.

Project 112 2003. *DeploymentLink* . (Last updated December 2, 2003)
[http://deploymentlink.osd.mil/pdfs/big_jack_a.pdf]

Satoh, et al. 2002. Perspectives on cadmium toxicity research. *Tohoku J.Exp.Med.* Vol. 196(1): 23-32.

Since there are a plethora of studies on cadmium toxicity and poisoning in laboratory animals and humans, we have limited this review to studies that are relevant to human health issues by focusing on carcinogenicity, genotoxicity, circulatory disease, nephrotoxicity and life expectancy. Cadmium exposure has been established to induce cancer in various tissues of laboratory animals. Contrary to early findings of the lack of genotoxicity by cadmium, recent findings of mammalian cell culture studies have revealed genotoxic effects. Furthermore, cadmium exposure at relatively low doses induces circulatory diseases in laboratory animals. Despite such results of various cadmium toxicities in animal studies, data from human studies are lacking and insufficient to support the cause-effect relationship. Although cadmium is currently considered to be a human carcinogen by the International Agency for Research and Cancer, it is inappropriate to conclude that sufficient evidence on the carcinogenicity of cadmium in humans exists. It is also thought that epidemiological studies so far reported do not support the occurrence of cadmium-induced circulatory disease in humans. Since there are inconsistent reports on the relationship of cadmium exposure with the life expectancy of people living in cadmium-polluted areas, further studies are needed for clarification. It is also necessary to examine apparent discrepancies in result between humans and experimental animals. It has been established that long-term exposure to cadmium causes renal dysfunction in both humans and experimental animals, and whether there are any differences in the inducibility of metallothionein in the kidney warrants further study.

Waalkes. 2003. Cadmium carcinogenesis. *Mutat.Res.* Vol. 533(1-2): 107-120.

Cadmium is a heavy metal of considerable environmental and occupational concern. Cadmium compounds are classified as human carcinogens by several regulatory agencies. The most convincing data that cadmium is carcinogenic in humans comes from studies indicating occupational cadmium exposure is associated with lung cancer.

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Cadmium exposure has also been linked to human prostate and renal cancer, although this linkage is weaker than for lung cancer. Other target sites of cadmium carcinogenesis in humans, such as liver, pancreas and stomach, are considered equivocal. In animals, cadmium effectively induces cancers at multiple sites and by various routes. Cadmium inhalation in rats induces pulmonary adenocarcinomas, in accord with its role in human lung cancer. Cadmium can induce tumors and/or preneoplastic lesions within the rat prostate after ingestion or injection. At relatively high doses, cadmium induces benign testicular tumors in rats, but these appear to be due to early toxic lesions and loss of testicular function, rather than from a specific carcinogenic effect of cadmium. Like many other metals, cadmium salts will induce mesenchymal tumors at the site of subcutaneous (s.c.) or intramuscular (i.m.) injections, but the human relevance of these is dubious. Other targets of cadmium in rodents include the liver, adrenal, pancreas, pituitary, and hematopoietic system. With the exception of testicular tumors in rodents, the mechanisms of cadmium carcinogenesis are poorly defined. Cadmium can cause any number of molecular lesions that would be relevant to oncogenesis in various cellular model systems. Most studies indicate cadmium is poorly mutagenic and probably acts through indirect or epigenetic mechanisms, potentially including aberrant activation of oncogenes and suppression of apoptosis.

Waalkes. 2000. Cadmium carcinogenesis in review. *J.Inorg.Biochem.* Vol. 79(1-4): 241-244.

Cadmium is an inorganic toxicant of great environmental and occupational concern which was classified as a human carcinogen in 1993. Occupational cadmium exposure is associated with lung cancer in humans. Cadmium exposure has also, on occasion, been linked to human prostate cancer. The epidemiological data linking cadmium and pulmonary cancer are much stronger than for prostatic cancer. Other target sites for cadmium carcinogenesis in humans (liver, kidney, stomach) are considered equivocal. In rodents, cadmium causes tumors at several sites and by various routes. Cadmium inhalation in rats results in pulmonary adenocarcinomas, supporting a role in human lung cancer. Prostate tumors and preneoplastic proliferative lesions can be induced in rats after cadmium ingestion or injection. Prostatic carcinogenesis in rats occurs only at cadmium doses below those that induce chronic degeneration and dysfunction of the testes, a well-known effect of cadmium, confirming the androgen dependency of prostate tumors. Other targets of cadmium in rodents include the testes, adrenals, injection sites, and hematopoietic system. Various treatments can modify cadmium carcinogenesis including supplemental zinc, which prevents cadmium-induced injection site and testicular tumors while facilitating prostatic tumors. Cadmium is poorly mutagenic and probably acts through indirect mechanisms, although the precise mechanisms remain unknown.

Waisberg, et al. 2003. Molecular and cellular mechanisms of cadmium carcinogenesis. *Toxicology.* Vol. 192(2-3): 95-117.

Cadmium is a heavy metal, which is widely used in industry, affecting human health through occupational and environmental exposure. In mammals, it exerts multiple toxic effects and has been classified as a human carcinogen by the International Agency for Research on Cancer. Cadmium affects cell proliferation, differentiation, apoptosis and

other cellular activities. Cd²⁺ does not catalyze Fenton-type reactions because it does not accept or donate electrons under physiological conditions, and it is only weakly genotoxic. Hence, indirect mechanisms are implicated in the carcinogenicity of cadmium. In this review multiple mechanisms are discussed, such as modulation of gene expression and signal transduction, interference with enzymes of the cellular antioxidant system and generation of reactive oxygen species (ROS), inhibition of DNA repair and DNA methylation, role in apoptosis and disruption of E-cadherin-mediated cell-cell adhesion. Cadmium affects both gene transcription and translation. The major mechanisms of gene induction by cadmium known so far are modulation of cellular signal transduction pathways by enhancement of protein phosphorylation and activation of transcription and translation factors. Cadmium interferes with antioxidant defense mechanisms and stimulates the production of reactive oxygen species, which may act as signaling molecules in the induction of gene expression and apoptosis. The inhibition of DNA repair processes by cadmium represents a mechanism by which cadmium enhances the genotoxicity of other agents and may contribute to the tumor initiation by this metal. The disruption of E-cadherin-mediated cell-cell adhesion by cadmium probably further stimulates the development of tumors. It becomes clear that there exist multiple mechanisms which contribute to the carcinogenicity of cadmium, although the relative weights of these contributions are difficult to estimate.

Weinbrenner, et al. 1998. Fostriecin, an inhibitor of protein phosphatase 2A, limits myocardial infarct size even when administered after onset of ischemia. *Circulation*. Vol. 98(9): 899-905.

BACKGROUND: The role of protein phosphatases (PPs) during ischemic preconditioning in the rabbit heart was examined. **METHODS AND RESULTS:** Fostriecin, a potent inhibitor of PP2A, was administered to isolated rabbit hearts starting either 15 minutes before or 10 minutes after the onset of a 30-minute period of regional ischemia and continuing until the onset of reperfusion. After 2 hours of reperfusion, infarct size was measured with triphenyltetrazolium chloride. In a second study with isolated rabbit cardiomyocytes, the effect of fostriecin pretreatment was assessed by measuring changes in cell osmotic fragility during simulated ischemia. PP1 and PP2A activities of isolated control and ischemically preconditioned cells were also measured. In a third series of experiments, left ventricular biopsies of isolated rabbit hearts were obtained before and at selected times during 60 minutes of global ischemia, and the tissue was assayed for PP1 and PP2A activities. In isolated hearts pretreated with fostriecin, only 8% of the ischemic zone infarcted, significantly less than that in untreated control hearts (33%; P<0.001) but comparable to that in ischemically preconditioned hearts (9%; P<0.001 versus control). Significant protection was also observed in the hearts treated only after the onset of ischemia (18% infarction; P<0.05 versus control). In isolated myocytes, fostriecin also provided protection comparable to that produced by metabolic preconditioning. Preconditioning had no apparent effect on the activity of either PP1 or PP2A in isolated ventricular myocytes or ventricular tissue obtained from heart biopsies. **CONCLUSIONS:** Fostriecin, a potent inhibitor of PP2A, can protect the rabbit heart from infarction even when administered after the onset of ischemia. But

inhibition of either PP1 or PP2A does not appear to be the mechanism of protection from ischemic preconditioning.

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Yue, et al. 2001. Menadione mimics the infarct-limiting effect of preconditioning in isolated rat hearts. *Am.J.Physiol.Heart Circ.Physiol.* Vol. 281(2): H590-5.

The role of mitochondrial free radicals in the cardioprotective effect of ischemic preconditioning was examined in isolated buffer-perfused rat hearts. Infarct size in control rat hearts subjected to 30 min of regional ischemia and 120 min of reperfusion was 32.6 +/- 3.4% of the risk zone. Ischemic preconditioning (3 cycles of 5-min global ischemia/5-min reperfusion) before the same regional ischemia and reperfusion protocol significantly reduced infarct size to 2.6 +/- 0.8% of the risk zone. Perfusion with menadione (3.0 microM), a generator of mitochondrial free radicals, in lieu of preconditioning ischemia significantly reduced infarction to 10.9 +/- 2.7%. N-2-mercaptopropionylglycine (1.0 mM), a free radical scavenger, blocked the protection of menadione, significantly increasing infarction to 23.5 +/- 1.1%. Myxothiazol (0.6 microM), a site III mitochondrial inhibitor, blocked the protection of menadione and significantly increased infarction to 25.2 +/- 3.8%. The infarct-limiting effect of menadione was attenuated to 19.7 +/- 1.5% of the risk zone by 10 microM SB203580, a

p38 mitogen-activated protein kinase (MAPK) inhibitor. Furthermore, menadione significantly increased p38 MAPK phosphorylation to a level 5.6-fold over basal. These results indicate that free radicals that originate within mitochondria can activate p38 MAPK and protect hearts against infarction.