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DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-10-17916	88100000245	4/23/10

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MR#326399

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Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency, ICC Building
1201 Constitution Ave., NW
Washington, DC 20004

Dear 8(e) Coordinator:

N,N-Dimethylacetamide
127-19-5

Please find enclosed a copy of a report that summarizes unpublished studies and personal communications, prepared by Henry J. Horn (July 20, 1959), on the above-identified substance.

The report makes reference to several studies, including published and unpublished studies not sponsored by DuPont that may contain information, previously unknown to EPA, that meets criteria for reporting under TSCA §8(e).

Sincerely,

A. Michael Kaplan, Ph.D.
Director - Regulatory Affairs

8EHQ-10-17916

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Attachment: 20 pages

8EHQ-0410-17916A
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HAZLETON LABORATORIES

Incorporated

FALLS CHURCH, VIRGINIA PALO ALTO, CALIFORNIA

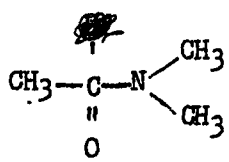
Sponsor: The Chemstrand Corporation Date: July 20, 1959

Material: Dimethylacetamide Lot No:

Subject: Compendium of Toxicology

INTRODUCTION

Dimethylacetamide (DMA), also known as acetyldimethylamine and (solvent CR) is a clear, neutral liquid having a specific gravity of 0.943, boiling point of 165.5°C. and a molecular weight of 87.12. Its structural formula is as follows:



It is infinitely soluble in water (mixing DMA in water produces heat) and alcohol, and very soluble in organic solvents and mineral oil. Because of its increased use as a commercial solvent and hence, the increased number of workers exposed to this material, it is necessary to understand the toxicology of DMA.

RELATED COMPOUNDS

An extensive search of the published literature has been fruitless concerning the toxicology of DMA. A related compound, diethylacetamide, has been studied by Bovet(1) in the prevention of traumatic shock in rats. It

was found that diethylacetamide increased mean survival time from three hours and 24 minutes to 10 hours and 50 minutes, following traumatic shock. The diethylacetamide was reported as having an intraperitoneal lethal dose as high as 3.0 g/kg in mice. Dimethylacetamide was found ineffective for this purpose and apparently was not studied.

Another related chemical, dimethylformamide, has been investigated by Massman(10). Dimethylformamide was found to be moderately toxic to mice, rats, rabbits, and cats with an LD_{50} of 1.4 to 3.7 ml/kg, depending on the route of administration. Liver damage (fatty degeneration and necrosis) was the outstanding pathological finding, with some accompanying kidney damage. Inhalation toxicology was investigated by exposing cats and rats to vapor concentrations of 100, 230, and 450 parts per million (ppm), eight hours daily, six days a week for 120 days. The only sign of toxicity was observed at the highest concentration where cats had anorexia and weight loss. An irregular incidence of liver necrosis was observed in rats, while in the cats, fatty degeneration of the liver was observed. The dimethylformamide was found to be readily absorbed by the intact skin. Applied for 24 hours on a soaked rag or painted daily for 28 days, dimethylformamide had no more than a transient slightly irritant effect on human skin. In another series of studies(11), the dermal LD_{50} value (guinea pigs?) of dimethylformamide was found to lie between 2.5 and 5.0 ml/kg. Three-week dermal applications to guinea pigs produced no deaths and only slight skin irritation.

DIMETHYLACETAMIDE

Acute Oral

In a series of unpublished studies(11) on DMA, the oral LD_{50} in mice was found to lie between 4.0 to 5.0 g/kg. Another unpublished series of studies by Kettering Laboratory(8) reported the minimum lethal dose of undiluted DMA to rabbits to be between 1.4 and 2.1 ml/kg.

Intraperitoneal

The acute intraperitoneal(11) LD_{50} in mice was found to lie between 3.2 to 4.0 g/kg, and the acute intraperitoneal(11) LD_{50} in rats between 2.0 and 2.5 g/kg. A repeated intraperitoneal study(11) was also performed on rats in which a fractional part of the LD_{50} was administered daily. Doses as high as 800 mg/kg were administered before death resulted after 25 days. Autopsies indicated that there was chemical peritonitis but no significant finding of lung, kidney, or liver damage was found. However, the results of microscopic evaluation of these organs were not available.

Acute Intravenous

In other unpublished studies(12), it was found that the acute intravenous LD_{50} in rats of the 100% DMA was 2.0 ml/kg, while the LD_{50} of a 50% aqueous solution was 6.7 ml/kg. In these studies, the low level rats remained normal; the intermediate rats showed incoordination and dyspnea, while the high level rats died rapidly with respiratory failure. The survivors from this study appeared normal within 24 hours.

Acute intravenous administration to dogs(12) of a 50% solution of DMA at doses of 0.5, 1.0, 1.5, and 2.0 ml/kg produced little or no

toxicity, even at the highest dosage level. However, a dose of 1.0 ml/kg of the 100% material produced death from respiratory failure within four minutes. In another acute intravenous administration(13) to dogs (strength of the DMA solution was not given) single doses of 2.0, 2.5, and 3.0 ml/kg produced stiffness and incoordination at the highest level. The major finding was increased respiration rate with some increase in temperature and pulse rate. All dogs were normal within three hours. Blood counts taken a week later were within normal limits.

Blood coagulation times were followed(12) in dogs receiving single intravenous doses of 50% aqueous solution of DMA. One dog received a 1.0 ml. total dose, another dog received 2.0 ml. total dose, while a third dog received 1.0 ml/kg. All three showed no effect upon blood coagulation time. A fourth dog received 2.0 ml/kg, and within one hour clotting time was reduced to one half of the control value, and continued to decrease to one quarter of the control value. The decreased clotting time persisted for 24 hours.

Chronic Intravenous

Chronic intravenous administration(12), in which two dogs received a 50% aqueous solution of DMA in doses of either 0.1 or 0.2 ml/kg twice daily for five days, produced no signs of toxicity.

Eight dogs received(14) a 50% aqueous solution of DMA at doses ranging from 0.1 to 2.0 ml/kg, given two times daily. One dog tolerated 0.1 ml/kg for 97 injections over a 72-day period. The dog vomited once during the study. Two dogs received 0.25 ml/kg twice daily. One of these was sacrificed after the ninth injection and showed a BSP retention of 46%. The other dog received 69 injections, during which time he vomited three times and showed anorexia, incoordination, and weakness. The BSP retention

increased to 36% but the dog returned to normal during a three-week recovery period. Three dogs received 0.5 ml/kg twice daily; two died after 13 injections and the other died after the 36th injection. Both showed incoordination, vomiting, raw bloody areas of mouth and gums, and eventually became prostrate and comatose. The BSP retention was between 45 and 70% in these dogs. The third dog, after receiving 15 injections, had the dosage schedule changed to once daily, but nevertheless continued downhill and after nine more injections was taken off the study. This particular dog was carried for an additional observation period of nine months with periodic liver biopsies during which time the dog gradually returned to normal. One dog received 1.0 ml/kg two times daily and died after the seventh injection. Another dog receiving 2.0 ml/kg two times daily died after five injections. In these animals receiving intravenous injections, the veins became sclerosed and occluded. Apparently, there was no recanalization of the veins. Furthermore, the livers were grossly yellow, the red blood cells and hemoglobin were decreased, and the white blood cell count was increased.

Acute and Chronic Subcutaneous and Intramuscular

Subcutaneous and intramuscular studies were also performed(12) in dogs using a 50% aqueous solution. Total doses of 1.0 and 2.0 ml. were used. Ecchymosis in the tissues was produced in one dog; in the dog receiving 2.0 ml. intramuscularly, severe hemorrhage, and necrosis occurred. Chronic subcutaneous(13) studies were also performed. In one of these studies, dogs received repeated subcutaneous administration of a 50% aqueous solution, at doses of 4.0 ml. twice a day for 19 days. The injections were apparently painful but otherwise no signs of toxicity were observed. Blood and urine values were within normal limits.

A similar study, in which 5.0 ml. was administered twice daily, resulted in some weight loss. Although the duration of the study is not known, it is stated that the study was terminated earlier than anticipated because the dogs became too difficult to handle, apparently because of the pain. At the site of injection, there was moderate to severe hemorrhage, congestion, induration, and slight necrosis in some animals, while multiple sterile abscesses and liquefaction necrosis was present in others. Microscopic examination of the liver of the highest level dogs showed periportal fatty metamorphosis, congestion and cloudy swelling of the centrolobular cells, with some edema. The low level dogs showed a similar but less severe picture.

In another chronic subcutaneous administration(13) study using a 1% aqueous solution of DMA, one dog received 100 ml. daily, five days a week, for a total of 21 injections over a 29-day period. Not as much pain accompanied these injections as with the 50% solution. However, it did cause marked decrease in red blood cell and hemoglobin, slight weight loss, and at the site of injection slight swelling and induration. Microscopic examination of the liver showed mild fatty metamorphosis, and mild centrolobular swelling and congestion. There was slight edema, scattered acute and chronic pericentral inflammatory reaction. In addition, the Kupffer cells were increased in number and the nuclei of the bile duct cells were pycnotic and distorted. There was also chronic ascending glomerulonephritis of the kidney.

Acute Dermal

The dermal(8) LD_{50} in rabbits was found to lie between 2.5 and 3.6 ml/kg for pure DMA following a 24-hour exposure, while a similar exposure using a 61.9% aqueous DMA solution yielded an LD_{50} between 3.6 and 6.0 ml/kg.

Dermal contact produced edema, hyperemia, and acute inflammation of the skin. Sublethal doses produced degeneration of heart, liver, and kidney while lethal doses also produced degeneration of the brain.

Further studies(11) were also performed on guinea pigs in which the DMA was applied under a suitable cuff and left in contact with the skin for 24 hours. Doses of 1.0 to 10 ml/kg were used. It was stated that doses less than 1.0 ml/kg killed the guinea pigs. The results of these studies indicated that the material was a strong skin irritant, although the DMA did not produce sensitization in another study using guinea pigs.

Chronic Dermal

Two guinea pigs received repeated dermal applications of the undiluted material at a dosage level of 1.0 ml/kg/day. One animal died after 12 days and the other survived 30 days(11).

Two milliliters of undiluted DMA were kept in contact with the unabraded abdominal skin(8) of each of three rabbits for two hours daily, five days a week over a period of 70 days (50 exposures). An additional three rabbits each received four milliliters of a 61.9% aqueous solution of DMA. The experimental procedure was identical to the previous. All animals were sacrificed within one to 14 days after the last application. There were no mortalities during the course of the study.

The skin of the animals subjected to the undiluted material became scaly, dry, hardened, and fissured, while the aqueous solution failed to induce these changes. No other signs of toxicity were observed.

Microscopic examination of the skin of the animals receiving the undiluted material showed chronic inflammation in those animals sacrificed

after the termination of the experiment, while in those which were maintained for an additional two weeks, there was no microscopic evidence of residual effect. The skin of rabbits exposed to the aqueous solution showed only slight acute inflammation. No lesions of any of the other organs were observed.

Hazleton Laboratories, Inc. performed repeated dermal applications on dogs. Two dogs per dosage level were used and the following levels were studied: 4.0, 1.0, 0.316, and 0.100 ml/kg/day. The DMA was rubbed into the skin of the clipped backs of the dogs and allowed to remain for five hours, following which the animals were bathed to be sure all traces of the DMA had been removed. Dogs receiving 4.0 and 1.0 ml/kg/day(2) showed progressive impairment of health. One of the dogs on the 4.0 ml/kg/day level died on the 15th day and the second dog was in such poor health that it was sacrificed on the 16th day. Both dogs at the 1.0 ml/kg/day level showed marked signs of toxicity after six weeks of repeated applications and were sacrificed for microscopic examination. The dogs in both high levels developed depression, weakness, ataxia, and abdominal tenderness. Diarrhea and jaundice were present in the dogs on the 4.0 ml/kg/day level just prior to death. Dogs at both high levels showed weight loss, and mild to moderate skin irritation. At termination of the studies, the dogs showed fissuring and thick scales, which resembled eschars. Hematological results were consistent with dehydration and showed an increase in hemoglobin and hematocrit. The dogs at the highest dosage level showed leukocytosis with an increase in the polymorphonuclear leukocytes, but with a slight shift to the left. Other outstanding findings were increased BSP retention at 15 and 30 minutes, and an increase in the

alkaline phosphatase. The DMA blood levels varied between 12.3 and 55.6 mg.% at the 1.0 ml/kg/day level and between 97.5 and 178 mg.% at the 4.0 ml/kg/day level. Urine analyses showed an increase in the white blood cells in the urinary sediment. Gross examination of the dogs on the 4.0 ml/kg/day level showed yellow livers, while at the 1.0 ml/kg/day level the livers appeared pale. At the highest dosage level, there was also a black fluid throughout the gastrointestinal tract. Microscopic examination of the highest dosage level revealed extreme fatty degeneration of the liver, while at 1.0 ml/kg/day level only one dog showed significant fatty degeneration. The kidneys of the animals of both levels were not remarkable. The section of skin which was examined from the 1.0 mg/kg/day level was slightly thickened and mildly infiltrated.

The dermal exposure at 0.316 and 0.100 ml/kg/day(5) was performed in the same manner as described above, except that it was continued for six months. One of two dogs on the 0.316 ml/kg/day level lost more than two kilograms of body weight by the end of the second month, but recovered over 90% of this loss by the end of the study. The other dog developed an ulcer at the site of application after four months. Administration to this site was stopped and the ulcer gradually healed over a period of one month. The skin of both dogs showed marked scaliness. There were no significant hematological and biochemical findings, except that one dog at the 0.316 ml/kg/day level showed a significant BSP retention and an increase in alkaline phosphatase concurrent with the decrease in body weight. In the latter part of the study, no significant findings were observed. Apparently the skin became toughened and less DMA was absorbed in the latter part of the study. The level of DMA in the blood seemed to correspond with these findings in this dog; however in

general, DMA in the blood was proportional to the level of dermal application. The following table presents these blood level ranges with dosage levels:

Dermal Dosage Level ml/kg/day	DMA in Blood mg. %
4.0	97.5 - 178
1.0	12.3 - 55.6
0.316	0.17 - 5.50
0.100	0.04 - 0.92

Gross examination of the organs of the animals at the 0.316 ml/kg/day level and 0.100 ml/kg/day level revealed them to be within normal limits. Microscopic examination of the liver of the experimental dogs showed slightly reticulated cytoplasm which increased proportional to dosage level. No significant microscopic findings were seen in the skin, except for slight thickening and/or inflammatory reaction.

Acute Eye Irritation

Eye studies(12) in two rabbits which received three drops of a 50% aqueous solution showed severe erythema, lacrimation, and edema.

Acute and Subacute Inhalation

In an acute inhalation study(7) at 575 ppm, two cats, two guinea pigs, four rabbits, two rats, and 10 mice were exposed. All animals survived the seven hour exposure, except nine mice which died between one to 16 hours after the exposure. The mice showed a marked loss of body weight. One cat sacrificed two days after the exposure showed parenchymatous degeneration of the liver and convoluted tubules of the kidney. The other cat sacrificed 17 days after the exposure was normal upon gross autopsy. No microscopic

work was done on this animal. The guinea pigs sacrificed two days after the exposure had the same findings as the first cat. The lungs of the three mice examined showed minute hemorrhagic areas. Microscopic examination showed parenchymatous degeneration of the liver and renal tubules. One rabbit was sacrificed two days after the exposure. Microscopic examination showed degeneration of the liver, necrosis, destruction of the nuclei, and degeneration of the renal tubules. Two rabbits were sacrificed after 17 days; one showed marked fatty degeneration of the liver, while the second showed only slight diffuse degeneration. The kidneys of both rabbits were within normal limits. Gross examination only of the rats revealed no abnormalities.

An acute inhalation study(7) at 406 ppm for seven hours was also conducted. Two cats, two guinea pigs, and four rabbits survived the exposure. Two rats died within 17 hours after termination of the study. Two cats were normal upon gross and microscopic examination. One guinea pig sacrificed three days after the exposure was normal upon gross and microscopic examination. The one rabbit examined after three days showed parenchymatous degeneration of the liver. The rat examined also showed parenchymatous degeneration of the liver.

In an experiment(7) of 3.5 hours at 406 ppm, six mice survived, three died within 16 hours and another died five days after termination of the exposure. Two mice examined microscopically showed marked parenchymatous degeneration and associated fatty degeneration of the liver, and considerable parenchymatous degeneration of the renal tubules. The lungs were congested and one animal had foci of recent hemorrhage.

In a subacute study(7) at 475 ppm, conducted seven hours daily for five days, two guinea pigs survived. All other animals died before the start of the fifth exposure. Two cats died after the third exposure; two rats after the second and third; and four rabbits after the second, third, and fourth exposures. Of the ten mice, six died after the first exposure, three after the second, and one after the third. A second group of 10 mice was initiated on the fourth day and were found dead the following morning. The mice exhibited labored respiration, followed by prostration after one or two hours of exposure. In the cats, slight salivation, occasional coughing and failure to eat were noted. Microscopic examination of the two cats that died after the third exposure, showed severe degenerative changes in the livers and kidneys. The lungs showed foci of atelectasis and other areas were emphysematous. There was moderate degeneration of the ganglion cells of the brain. The tissues of one mouse which died after the first exposure, showed slight pulmonary edema and congestion of the lungs, and parenchymatous degeneration of the liver, kidneys, and brain. The tissues of two rabbits were examined and in both there was marked degeneration of the hepatic cells of the liver with necrosis of the cells. There was severe degeneration of the renal tubules. In addition, the lungs showed areas of atelectasis, while the brain showed degenerative changes.

Chronic Inhalation

Animals were exposed(7) to 235 ppm of DMA seven hours per day, for 220 days. Two cats, two guinea pigs, and two rats survived throughout the entire period. Of four rabbits, three died after the eighth, 54th, and 117th exposure. Two others subsequently added to the experimental group

survived until the end of the experiment, having been exposed 95 and 141 times respectively. All of the original 10 mice died and were replaced at various times. In all, 25 mice died, 11 survived, and three disappeared.

No signs of intoxication were observed in any of the animals, except the mice and rabbits which died. These deaths followed respiratory distress and prostration. Microscopic examination of the cats showed changes in the liver and spleen. There was fatty degeneration and diffuse parenchymatous degeneration of the liver. The Kupffer cells had large amounts of hemosiderin stored within them. The spleen of one cat contained a large amount of hemosiderin within the macrophages. The guinea pig that was sacrificed five days after the study terminated was found to have normal tissues. The guinea pig sacrificed one month after the study terminated was found to have large quantities of hemosiderin deposited in the hepatic cells, in the cells lining the convoluted tubules of the kidneys, and in the cells of the reticular zone of the adrenal. There was also a small focus of necrosis in the liver, and diffuse degeneration of the cells lining the convoluted tubules of the kidneys. Of the three rabbits that died during the exposure, one died of an infection. In the other two, moderate degeneration of the liver and convoluted tubules of the kidney were seen. Of the rabbits that survived, changes were found in only one animal; these consisted of the deposition of moderate numbers of small granules of hemosiderin in the cells lining the distal convoluted tubules. The two surviving rats were examined microscopically and found to be normal in all respects. Severe degenerative changes in the liver and kidneys were found in representative mice that were examined. There was no apparent effect on the number of erythrocytes or in the hemoglobin of the animals exposed in this study.

In a study(8) at 103 ppm conducted seven hours per day for 150 exposures over a period of 215 days, one cat, one guinea pig, five male and five female mice, one rabbit, and two rats survived. An additional cat and three rabbits added from time to time survived after 140, 137, 126, and 98 periods of exposure, respectively. One guinea pig died from incidental causes. Three rabbits died after the ninth, 24th, and 52nd exposures. Microscopic examination of the cats showed slight interstitial pneumonitis. One guinea pig died of pulmonary infection, while the other showed slight degenerative changes of the brain and liver. The three rabbits that died exhibited diffuse degenerative changes in the brain, heart, liver, and kidney, together with edema, hyperemia, and interstitial pneumonitis of the lung. The lungs of the four surviving rabbits exhibited slight to moderate interstitial pneumonitis; however, the remaining tissues were normal. Tissues from two rats were normal but showed slight interstitial pneumonitis. Tissues from six mice showed pulmonary infection, while tissues from two showed kidney infection. Interstitial pneumonitis was also present in the control group.

Two cats, one guinea pig, five female mice, four rabbits, and two rats survived an exposure to 48.8 ppm(9) DMA seven hours a day, for 150 exposures, over a period of 213 days. One guinea pig and several mice died due to extraneous causes. No signs of toxicity were noted during the course of the study, and gross and microscopic pathology was negative.

Chronic inhalation studies(3, 4, 6) were performed at Hazleton Laboratories, Inc. using concentrations of 195, 103, 64.4, and 40.0 ppm of DMA. All four studies were performed over a period of six months on a six-hour-per-day, five-day-per-week basis. Each experimental group consisted of

two dogs and 20 rats. Two additional groups for control purposes were housed simultaneously in the laboratory. The concentration of DMA in the exposure chamber was determined frequently during the course of the studies by drawing known quantities of chamber atmosphere through gas washing bottles to trap the DMA. The concentration of DMA in the water was determined by its absorbancy at 220 millimicrons with a Beckman DU Spectrophotometer. At intervals throughout the studies, hematological and biochemical studies were performed on the dogs. These consisted of hemoglobin, sedimentation rate, hematocrit, WBC, differential smear, blood urea nitrogen, BSP retention, alkaline phosphatase, thymol turbidity, and urine analyses. Furthermore, the DMA levels of the blood in the dogs was determined by acid-hydrolysis to convert the DMA to dimethylamine. The dimethylamine was then measured spectrophotometrically by the method of Dowden (Dowden, H. C., Biochem. J. 32, 455, 1938).

Throughout all four studies no signs of toxicity were noted except in the rats exposed to the highest concentration. These rats presented an unkempt appearance with red-tinged discharge around the eyes. The experimental animals did not gain as much weight as the control animals. Mortality among the experimental animals in all groups was equivalent to that among the controls. The results of the hematological studies on all dogs from all studies revealed no significant changes in hemoglobin, sedimentation rate, hematocrit, WBC, or differential smear. Likewise, no significant differences were observed in the results of the urine analyses performed on the dogs during the study. Significant biochemical findings which consisted of BSP retention and elevated alkaline phosphatase were observed in the higher levels.

No significant findings were noted in blood urea nitrogen determinations or thymol turbidity tests. The DMA in the blood of the dogs was also examined as described previously using Dowden's method. The following table presents the range of values of BSP retention, alkaline phosphatase, and DMA blood level in the dogs.

Level ppm	Bromsulphalein 15 min.	Bromsulphalein 30 min.	Alkaline Phosphatase Units	DMA Blood Level Mg. %
195	0 - 12%	0 - 4%	0.28 - 6.40	2.18 - 23.4
103	0 - 6%	0 - 4%	0.40 - 2.48	0.75 - 13.8
64.4	0	0	0.33 - 0.81	0.62 - 0.95
40.0	0	0	0.52 - 1.06	0.60 - 0.80
Control	0	0	0.18 - 2.12	0.01 - 1.41

It will be observed that there is a general decrease in the blood DMA level with decrease in concentration of DMA to which the animals were exposed. Animals at the two lowest levels, 64.4 and 40.0 ppm, did not show significant BSP retention nor alkaline phosphatase, and likewise the dogs exposed to these two levels showed the lowest levels of DMA in the blood.

At termination of the exposures, the surviving experimental and control animals were sacrificed and gross autopsies were performed on all animals. Organs of the test rats did not appear to be significantly different from those of the control rats. In the dogs exposed to the highest level, one dog showed lungs which were slightly red on external surface and cut section. The livers were dark red in color, had a rough appearance, and seemed to be of leathery texture. The liver of the other dog had a slightly yellowish tinge. Otherwise, sections of all experimental dogs appeared to be comparable to those for their respective controls.

Microscopic examination of tissues from all dogs and from representative rats was made from all dosage levels and both control groups. The most outstanding findings were seen in the liver. Liver sections from control animals were within normal limits. Sections of liver from animals exposed to 195 ppm showed degeneration of the liver cord cells which was apparently periportal fatty metamorphosis. One of the dogs at the highest dosage level showed congestion and the liver changes were slightly more severe than the other dogs at this level. The dogs exposed to 100 ppm showed findings which were similar to those seen in the 195 ppm level. The animals exposed to 100 ppm showed periportal liver cell degeneration. The changes in one dog were slightly less severe than in the other dog at this same dosage level. At the two lower levels, only slight rarefaction (of varying degrees) of the cytoplasm was seen in the centrolobular liver cord cells. The degree of rarefaction might have been slightly greater in the 64.4 ppm group, but the differences were not considered significant. These findings in the low level dogs were not considered indicative of toxicity since they were comparable to the livers of the control dogs. Sections of lung from dogs exposed to DMA showed slight irritation which, in general, appeared only slightly greater than that seen in the control animals.

Microscopic examination of liver sections of the experimental rats showed, in the highest level, 195 PPM varying degrees of cytoplasmic disturbance, cholangitis, periangiitis, and small discrete areas of focal necrosis of the parenchymal cells. These areas of focal necrosis were circumscribed by a zone of leukocytic cells. Three of five rats at the 100 ppm level showed significant liver cell degeneration, while the remaining two showed only mild

changes. The liver cell degeneration in two of the three showing significant changes appeared to be moderate fatty degeneration, while the third appeared to be a mild albuminous degeneration. Changes of this nature were not observed in livers from the control rats. Sections of liver from all rats but one exposed to 64.4 ppm were within normal limits. In this rat, the centrolobular cord cells showed only minimal changes consisting of granular cytoplasm and slight swelling in comparison to the cord cells at the periphery of the liver lobules. Sections of liver from rats exposed to 40.0 ppm were within normal limits. Changes in the lungs of the rats were difficult to evaluate because of the pneumonia which was seen, even in control animals. In general, it appeared that the experimental animals showed some evidence of irritation from the exposure.

SUMMARY

Dimethylacetamide would appear to be a relatively non-toxic material on the basis of the results of acute oral, intraperitoneal, intravenous, and dermal studies. However, it has been found by numerous experiments that the material has an insidious toxicity on prolonged application. Repeated exposures produce liver damage which can be first recognized by an increased BSP retention, and eventually by frank jaundice. DMA is readily absorbed by all routes of contact. Human workers will probably be primarily subjected to DMA poisoning through dermal contact and inhalation exposure. Safety precautions for all workers should

include avoiding dermal contact with DMA and maintaining a concentration of not more than 30 parts per million in the atmosphere where humans are working.

Submitted by _____
HENRY J. HORN, M.D.

GC

R E F E R E N C E S

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11. Personal Communication from David Fassett.
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- No Signature Required — Package may be left without obtaining a signature for delivery
- Direct Signature — Someone at recipient's address may sign for delivery. ***Fee applies.***
- Indirect Signature — If no one is available at recipient's address, someone at a neighboring address may sign for delivery. For residential deliveries only. ***Fee applies***

Does this shipment contain dangerous goods?

- No
- Yes — As per attached Shipper's Declaration
- Yes — Shipper's Declaration not required
- Dry Ice — Dry ice - 9, UN 1845 ____ x ____ kg

Dangerous goods (including dry ice) cannot be shipped in FedEx packaging or placed in a FedEx Express Drop Box

- Cargo Aircraft Only

7 Payment ***Bill to:***

Enter FedEx Acct. No. or Credit Card No. below

- Sender — Acct. No. in Section 1 will be billed
- Recipient
- Third Party
- Credit Card
- Cash/Check

Total Packages _____ Total Weight _____ lbs. Credit Card Auth _____

*Our liability is limited to $100 unless you declare a higher value. See the current FedEx Service Guide for details.

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