PRM 20-26
(70FR34699)

(9)

From: James Salsman <james@readsay.com>
To: Michael Lesar <MTL@nrc.gov>
Date: Sun, Jul 23, 2006 4:09 AM
Subject: Re: Change of address and status update request

Dear Michael:

Thank you for your reply.

Recently, there have been multiple peer-reviewed medical publications concerning the neurotoxicity of uranium, which like reproductive and developmental toxicity, hasn't been considered in any exposure regulations. For example:

[1] Briner, W. and J. Murray (2005) "Effects of short-term and long-term depleted uranium exposure on open-field behavior and brain lipid oxidation in rats," Neurotoxicology and Teratology, vol. 27, pp. 135-44. http://www.bovik.org/du/du-on-rats.pdf

[2] Monleau, M. et al. (2005) "Bioaccumulation and behavioral effects of depleted uranium in rats exposed to repeated inhalations," Neuroscience Letters, vol. 390, pp. 31-6.

[3] Lestaevel, P. et al. (2005) "The brain is a target organ after acute exposure to depleted uranium" Toxicology, 212, 219-226. http://dx.doi.org/10.1016/j.tox.2005.05.002

[4] Jiang, G.C. and M. Aschner (2006) "Neurotoxicity of depleted uranium: reasons for increased concern," Biological Trace Element Research 110:1-18. PMID 16679544.

I am considering submitting another petition very similar to PRM-20-26 asking that this neurotoxicity information also be used to set exposure limits.

Instead of doing that, can the above citations be informally transmitted to the PRM-20-26 decision-makers, since the subject and necessary action is so similar? I don't want to formally amend the petition, since I know that might result in a re-opened comment period and further delays, but I am very interested in asking that the people who are already looking at previously unconsidered uranium toxicities to also consider neurotoxicity.

Is there a way to do that informally? Can I just ask that you forward this as if it was a late public comment? If so, please do.

Sincerely,
James Salsman

Michael T. Lesar wrote:

> We have not reached a final decision on whether your petition is to be
> granted or denied. The technical staff is carefully evaluating your
> request and the public comments received. Of course, the time for final
> action depends on that decision as rulemaking can be is a lengthly
> process.

Template= SECY-067

SECY-02

>
> >>> James Salsman <james@readsay.com> 07/12/2006 5:16 PM >>>
> Michael T. Lesar
> Chief, Rules and Directives Branch
> US Nuclear Regulatory Commission
>
> Dear Michael:
>
> I am the petitioner on PRM 20-26. Please note my new postal address:
>
> 353 Aldean Ave
> Mountain View, CA 94043
>
> My phone number (650.793.0162) is the same.
>
> Please send me a status update on PRM 20-26, including reference to
> process stages and anticipated or estimated duration(s) of the
> remaining stages. Please also let me know whether the issue of
> reproductive toxicity is considered an urgent matter by rulemaking
> staff. Thank you.
>
> Sincerely,
> James Salsman
>

CC: <tjlodge50@yahoo.com>, <Dlind49@aol.com>

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Neurotoxicology and Teratology 27 (2005) 135–144

NEUROTOXICOLOGY AND TERATOLOGY

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Effects of short-term and long-term depleted uranium exposure on open-field behavior and brain lipid oxidation in rats

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Available online 12 October 2004

Abstract

Male and female rats were exposed to depleted uranium acetate (DU) in drinking water at doses of 0, 75, or 150 mg/L for either 2 weeks or 6 months. After exposure, the animals were tested for behaviors in the open-field. After testing in the open-field, the brains were examined for levels of lipid oxidation using the thiobarbituric acid (TBA) assay. Behavioral differences (line crossing and rearing) were seen in male rats after 2 weeks exposure to DU in drinking water for the highest dose group. Increased brain lipid oxidation was seen for the highest dose group for both genders. Lipid oxidation levels correlated significantly with line crossing and rearing in the open-field. After 6 months exposure, behavioral differences for male rats in the open-field remained and expanded to include other behaviors (grooming, defecation, and urination). Female rats also demonstrated some behavioral changes after 6 months exposure. Lipid oxidation in the brain continued to be seen; however, these levels no longer correlated with open-field behaviors. These data suggest that DU is a toxin that crosses the blood–brain barrier, producing behavioral changes in male rats and lipid oxidation regardless of gender in as little as 2 weeks in the rat. Longer exposures to DU may produce greater behavioral changes but compensatory mechanisms may reduce the effects of lipid oxidation. Males appear to be more sensitive to the behavioral effects of DU.

Keywords: Depleted uranium; Behavior; Lipid oxidation

1. Introduction

Depleted uranium (DU) is a heavy metal by-product of enriching uranium for nuclear energy or nuclear weapons production. DU is chemically identical to native uranium but is 40% less radioactive than the parent element. There are some civil uses of DU, primarily in aircraft and watercraft where it is used as a stabilizer. However, the vast majority of DU is used by the military where, because of its pyrophoric properties and being of high density, it is used in armor and armor penetrating munitions. When used as a penetrator, DU combusts creating a mixture of DU compounds, primarily oxides, which are then deposited around the impact area.

Exposure to DU may occur when handling the weapons or armor, if struck by DU containing shrapnel, inhalation of DU dust, exposure of the skin to DU dust, or by oral ingestion of DU containing soil or dust. DU is primarily an alpha and beta particle emitter, and because of its low radioactivity, skin exposure of external regions of the body is of little concern. However, inhalation or ingestion of DU would allow direct exposure to DU's low-level radioactivity as well as direct chemical activity in the body. Thus, DU exposure by inhalation is probably the greatest route of exposure. Direct chemical activity of DU may be more of a concern than DU's radioactivity [1,21,22,28]. When DU is used as a kinetic energy penetrator, the explosive impact and combustion of DU produce a cloud of fine DU containing particulates that can remain in the air for several hours [6]. Roughly 50% of the particles in the cloud is respirable and lodges in the alveoli [25] and solublize, with DU entering the

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bloodstream for an extended period. Once DU has entered the alveoli, it may have a pulmonary half-life of nearly 4 years [12]. Exposure to DU may continue after the end of combat operations because DU has little mobility in the soil. This allows it to continue to be an exposure risk via inhaled or ingested dust. This problem of DU dust is reminiscent of lead dust, which continues to be a problem for urban populations in the United States even after discontinuing the use of leaded gasoline [20].

There is considerable interest in the potential chemical and radiologic toxicity of DU. DU munitions were used in the Persian Gulf War, the Kosovo police action, and the conflicts in Afghanistan and Iraq. It has been estimated that 320 tons of DU were deposited in Iraq soils during Desert Storm and an estimated 13 tons deposited in Kosovo. There are estimates that 176 tons of DU were used in the 2003 Iraq War. A great deal of public concern about DU toxicity has been generated in the United States and even more so in Europe and the Middle East. Much of the debate about the effects, or lack of effects, of DU is rhetorical because of the lack of empirical data on DU exposure. Human studies that focus on DU are lacking, most focus on "Gulf War Syndrome" (for reviews, see Refs. [10,11,14,15,26]), making the effects of DU difficult to discern. Few human studies have focused on DU only.

Human studies focusing on DU exposure have primarily been conducted on Gulf War veterans. Elevated DU levels were found in spot sampled urine of Gulf War veterans with retained DU fragments [13,18]. Another study found that lowered performance on computerized neuropsychological tests was related to urinary DU levels, as were elevated prolactin levels [18]. A study of an enlarged Gulf War cohort seemed to indicate urinary DU levels were not elevated in veterans that were simply present in the theater of war, unless DU fragments were embedded [17].

Most studies in animals have focused on the naturally occurring form of uranium [8], with comparatively few examining DU. Studies that have been done indicate that DU does cross the blood–brain barrier and accumulates in the central nervous system, including the hippocampus, where electrophysiologic changes have been demonstrated [16,24]. Preliminary studies in our laboratory have found that DU exposure in drinking water alters the development and behavior of mice and the open-field behavior of rats. These early studies also found evidence of oxidation of brain lipids in exposed mice [2–5].

In light of the evidence presented above, we set out to determine if DU exposure would produce behavioral effects in rats that would be both time and dose dependent. Additionally, we set out to determine if DU exposure would produce lipid oxidation of CNS structures. Lipid oxidation is one mechanism by which metals may exert their toxic effects [27].

2. Methods

Male and female Long–Evans rats were housed under standard laboratory conditions with a 12:12 light/dark cycle with ad libitum access to food and water. Animals were exposed to depleted uranium acetate dihydrate in drinking water at doses of 0, 75, or 150 mg/L for 2 weeks or for 6 months. These dosages were based on previous studies [9] using up to 50 mg/kg/day by gavage to produce teratogenic effects. Based on water consumption of 100 ml daily, this produced an approximate exposure of 50 or 25 mg/kg/day, well within the dosage range of other studies. These doses may appear exceptional, however, uranium is very heavy, 150 mg/L of uranyl acetate is equivalent to 0.35 mM, or 0.18 mM, for 75 mg/L. Human studies of human dosing with DU are not available in the literature. Mean ages and sample sizes are listed in Table 1.

At the conclusion of exposure, animals were tested in the open-field maze for a period of 5 min. The maze consisted of a painted wooden box (120 cm×120 cm×24 cm) with marked grid lines every 23 cm. Animals were scored on number of lines crossed, number of rears, number of instances of grooming, number of fecal boluses deposited and number of instances of urination. Experimenters were blind to the animal's experimental group.

After behavioral testing, animals were sacrificed with an overdose of chloroform, the brains extracted, weighed, and frozen at −20°C. Lipid oxidation was assayed using the thiobarbituric acid (TBA) assay [23]. Briefly, a weighed sample of frontal pole was homogenized and incubated with a solution of 3% TBA, 0.4 % SDS, and 7.7 % acetic acid, pH 3.5, at room temperature, overnight. After incubation, a mixture of butanol and pyridine (15:1) was introduced. The organic layer was removed and absorbance read at 532 nm. Concentrations were calculated against known concentrations of the standard malondialdehyde (MDA).

2.1. Chemical sources

Depleted uranium acetate dihydrate was obtained from Ted Pella (Redding, CA). All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO).

Statistical analysis was carried out using correlations and ANOVA with gender and dosage as independent variables using the program Statview v.5.0.1. Accumulation of error for multiple comparisons was controlled for with Fisher's

Table 1
Mean age in months and sample sizes for dosage and length of exposure

	Control	75 mg/L, 2 weeks	150 mg/L, 2 weeks	75 mg/L, 6 months	150 mg/L, 6 months
Age (months)	8.23	7.1	11.4	10.5	13.8
Number (*n*)	42	27	30	24	25

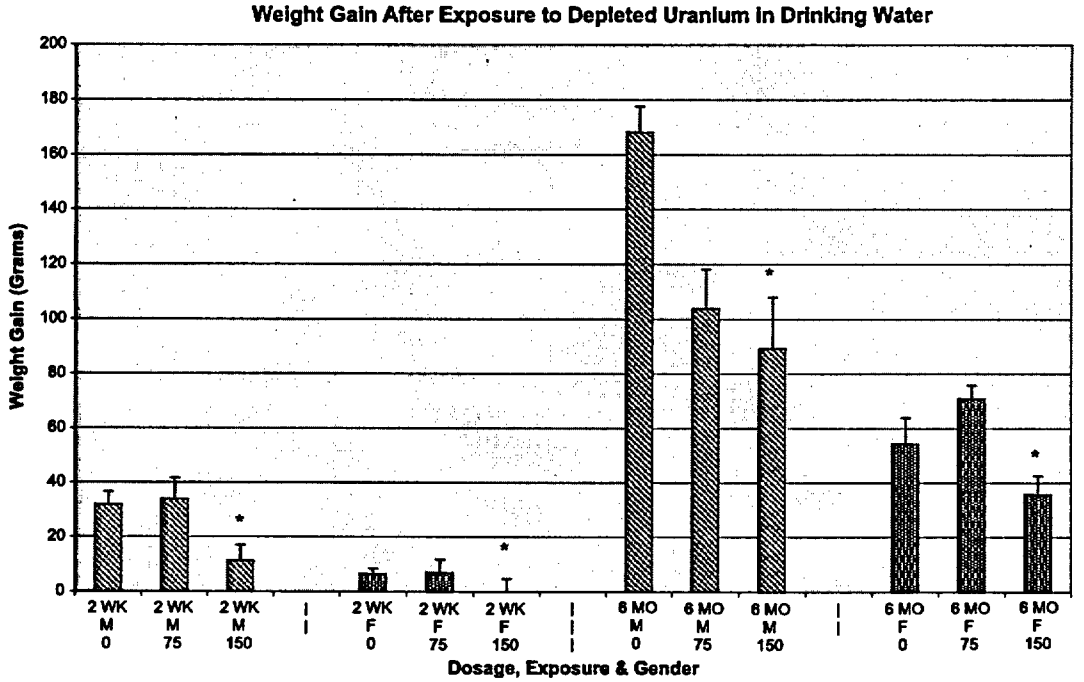

Fig. 1. Weight gain for male and female rats exposed to DU in drinking water for either 2 weeks or 6 months. Dosage (0, 75, or 150 mg/L) is seen along the *X*-axis. *Significantly ($p<0.05$) less weight gain for the 150 mg/L groups for both 2 weeks and 6 months of exposure than for controls. Error bars indicate S.E.M.

PLSD. A significance level of 0.05 was used for all tests, unless indicated otherwise. All control animals (those exposed to 0 mg/L, regardless of length of time) were treated as a single control group and the experimental groups compared to this larger group. For clarity, we break the analysis down into the length of exposure.

3. Results

After either 2 weeks exposure or 6 months exposure, all of the animals appeared to be generally healthy with no differences between the groups seen on casual examination. Noteworthy was that both male and female rats in the 150

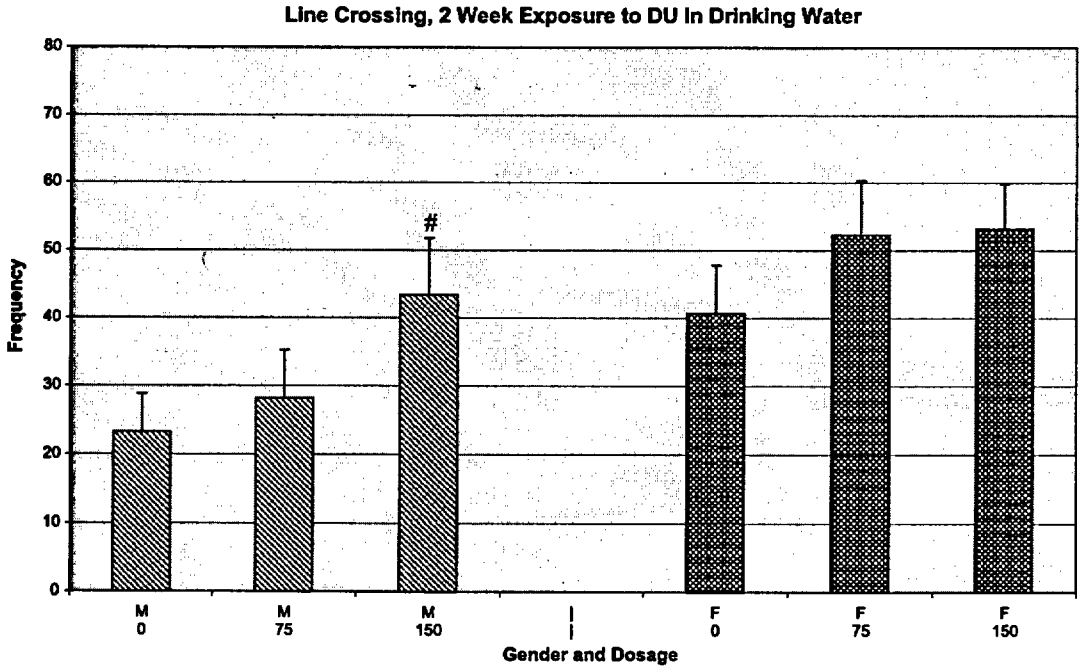

Fig. 2. Open-field line crossing for male and female rats exposed to DU at doses of 0, 75, or 150 mg/L for 2 weeks of length. The male 150 mg/L group demonstrated significantly more line crossing than the control groups ($^{\#}p<0.05$) compared to control with Fisher's PLSD following an *F* test trend of $p=0.07$. Error bars indicate S.E.M.

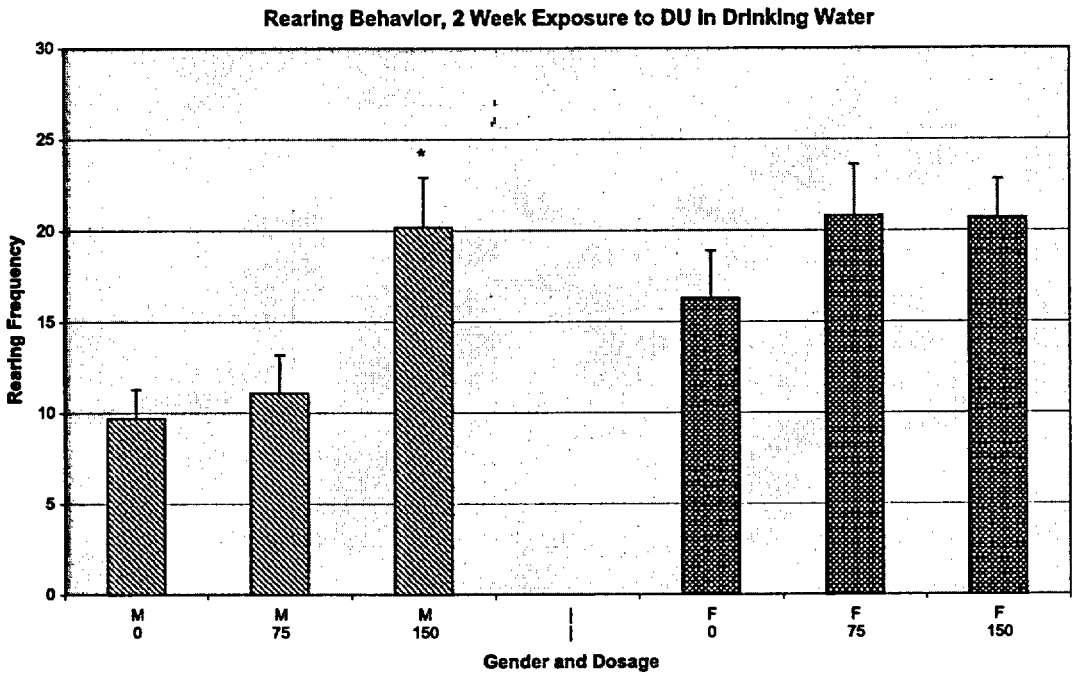

Fig. 3. Open-field rearing for male and female rats exposed to DU for 2 weeks. Doses and gender are indicated on the X-axis. The male 150 mg/L group demonstrated significantly more rearing than the control group (*$p<0.05$). Error bars indicate S.E.M.

mg/L group gained less weight at the end of either 2 weeks ($p=0.01$) or 6 months of exposure ($p=0.001$; Fig. 1).

3.1. Two-week exposure

Overall ANOVA for line crossing approached statistical significance [$F(2,90)=2.79$, $p=0.07$], with follow-up analysis indicating line crossing being greater for the male 150 mg/L DU-exposed group ($p=0.01$) with no gender interaction (Fig. 2). Rearing behavior was also different for the DU exposed groups [$F(2,90)=5.33$, $p=0.007$]. The male 150 mg/L group demonstrated statistical significance ($p=0.001$). There was no interaction with gender (Fig. 3).

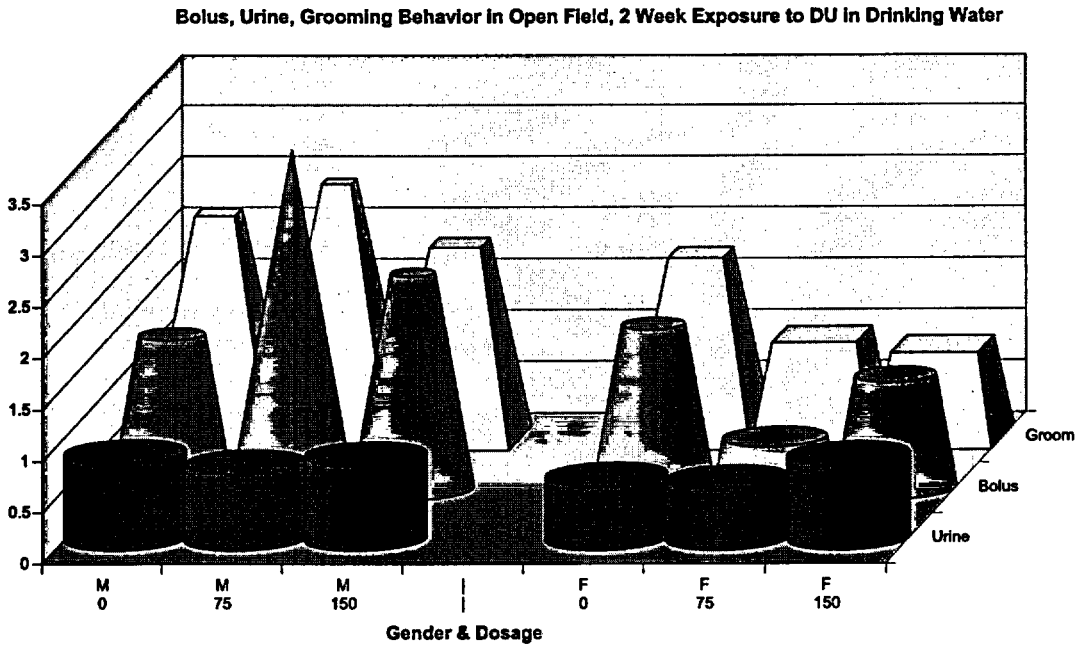

Fig. 4. Grooming, urination, and fecal bolus deposition for male and females rats exposed to DU for 2 weeks. Gender and dosage are indicated on the X-axis. There were no significant differences for any of the experimental groups.

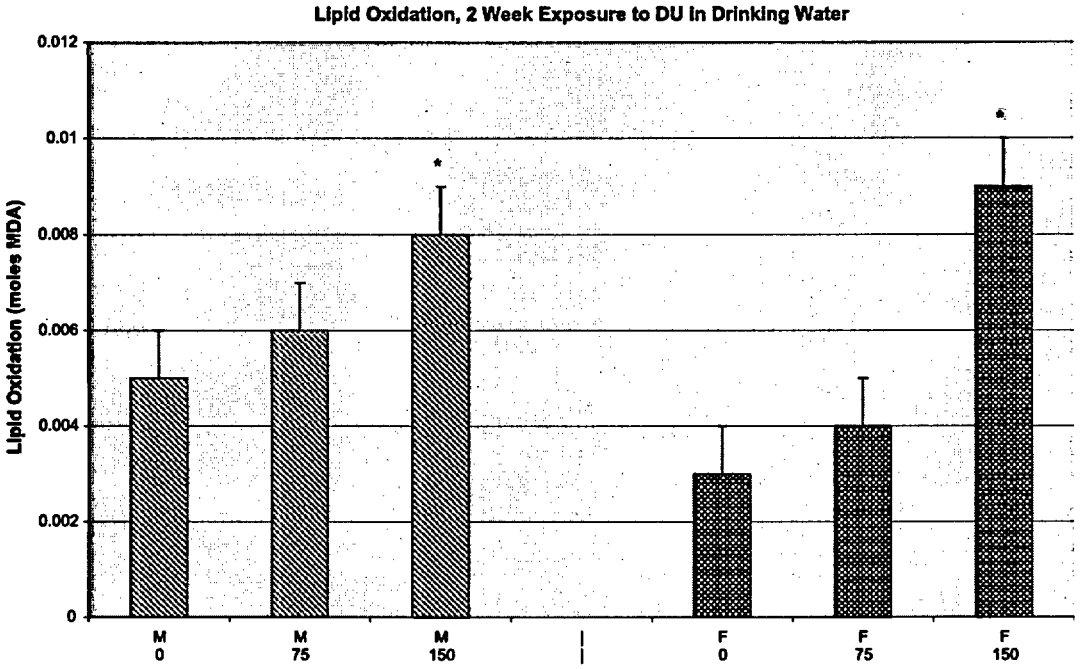

Fig. 5. Brain lipid oxidation in male and female rats exposed to either 0, 75, or 150 mg/L of DU for 2 weeks. *Y*-axis indicates lipid oxidation with reference to known concentrations of MDA. The 150 mg/L demonstrated significantly more lipid oxidation than the control group (*$p<0.05$). Error bars indicate S.E.M.

Other measured open-field behavior (urination, bolus deposits, grooming) did not demonstrate statistically significant effects for DU exposure (Fig. 4).

There was a statistically significant effect for lipid oxidation for both sexes [$F(2,90)=10.71$, $p<0.0001$], with the 150 mg/L group being different from control ($p<0.0001$; Fig. 5). Brain lipid oxidation formed statistically significant correlations with line crossing behavior ($r(94)=0.21$, $p<0.05$) and rearing behavior ($r(94)=0.23$, $p<0.05$) in the open-field (Fig. 6).

3.2. Six-month exposure

Overall analysis of line crossing behavior in rats after 6 months of exposure to DU revealed an effect of dose [$F(2,85)=7.50$, $p=0.001$], with the male 150 mg/L group

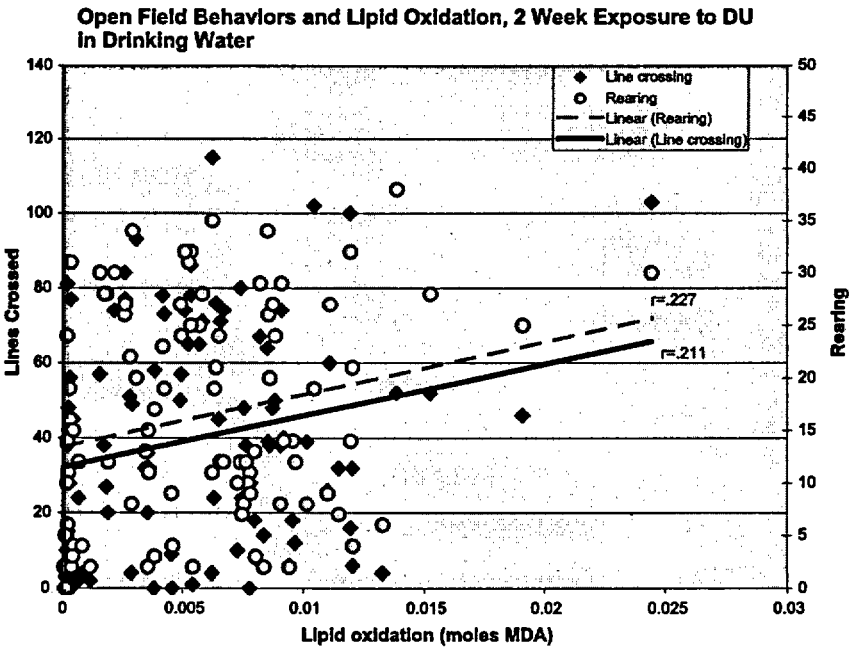

Fig. 6. Correlation and linear regression for brain lipid oxidation levels and rat line crossing and rearing behavior in the open-field. Both rearing and line crossing form significant correlations with lipid oxidation levels ($p<0.05$ for both). Brain lipid oxidation is expressed in terms of known concentrations of the standard MDA.

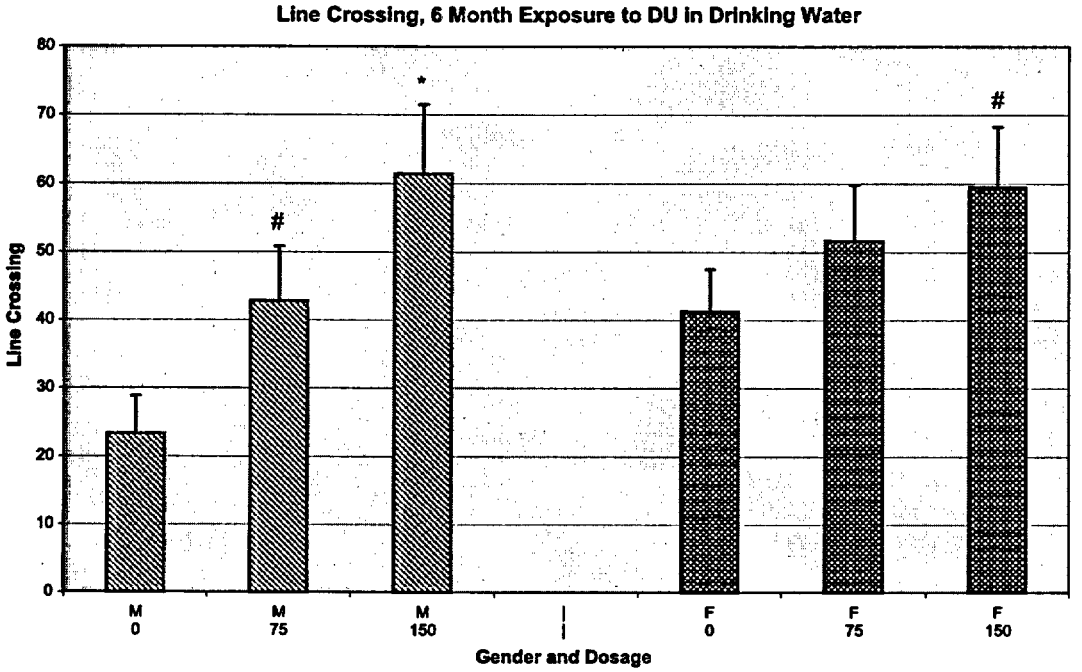

Fig. 7. Effects of 6 months of exposure to DU at 0, 75, or 150 mg/L on open-field line crossing in rats. The male 150 mg/L group significantly different from control at 0.05 (*); females at 150 mg/L and males at 75 mg/L reached a significance of 0.09 (#). Error bars indicate S.E.M.

being significantly different from control (p=0.0003). The male 75 mg/L group and the female 150 mg/L group demonstrated borderline effects at p=0.09. There was no interaction with gender (Fig. 7). There was also a dose effect for rearing behavior [$F(2,85)$=3.41, p=0.04], with the 75 mg/L group being marginally different from control (p=0.08) and the 150 mg/L group engaging in more rearing than controls (p=0.02; Fig. 8).

Exposure to DU for 6 months produced significant effects for bolus deposition [$F(2,85)$=6.854, p=0.002], with the male and female 150 mg/L group significantly different from control (p=0.02). There was no interaction with

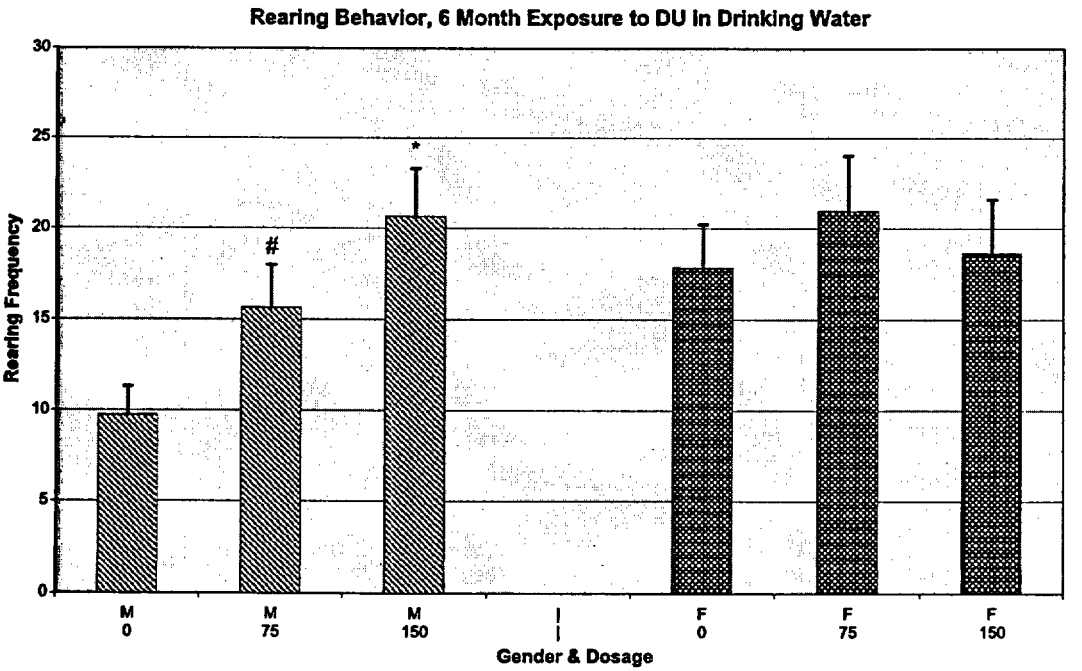

Fig. 8. Effects of 6 month of DU exposure on open-field rearing behavior of the rat. Dosage and gender are found on the X-axis. The male 150 mg/L group is significantly different from control (*p<0.05), the male 75 mg/L group approaches significance at p=8.08 (#). Error bars indicate S.E.M.

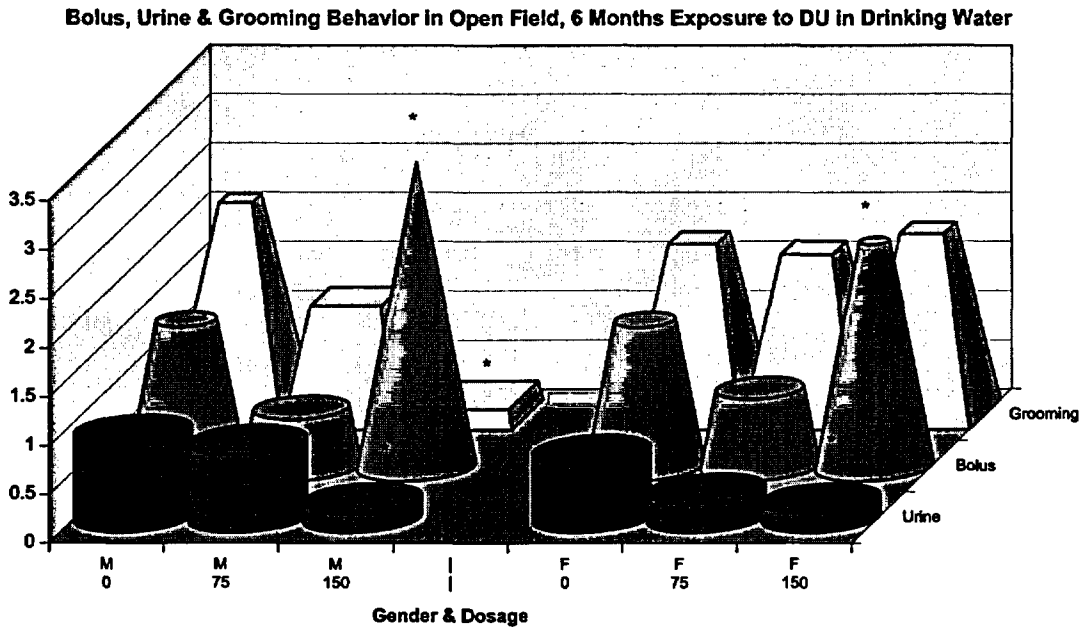

Fig. 9. Grooming, urination, and bolus deposition behaviors in the open-field for rats exposed to DU for 6 months. Gender and dosage are seen on the *X*-axis. Behaviors significantly different from control indicated by asterisk (*$p<0.05$).

gender. Urination was also affected [$F(2,85)=7.77$, $p=0.0008$) for both sexes with the 150 mg/L group significantly different from controls ($p=0.0002$). There was no interaction with gender. Lastly, grooming was effected by 6 months of DU exposure [$F(2,85)=3.21$, $p=0.045$], with the male 150 mg/L group being significantly different from control ($p=0.022$). There was a significant interaction between dose and gender [$F(2,85)=3.71$, $p=0.029$] for grooming (Fig. 9).

Six months of DU exposure had an overall marginal effect on brain lipid oxidation [$F(2,85)=2.51$, $p=0.09$], with the difference between control and the 150 mg/L group for both sexes reaching significance ($p=0.05$) on follow-up analysis. There was no interaction with gender (Fig. 10).

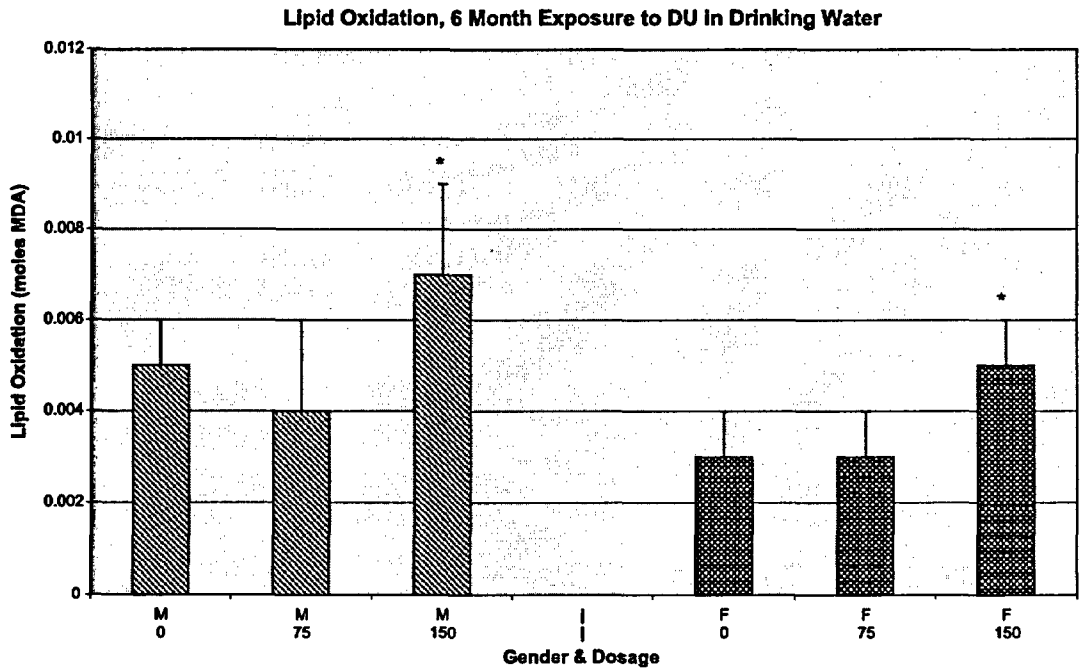

Fig. 10. Brain lipid oxidation in male and female rats exposed to either 0, 75, or 150 mg/L of DU for 6 months. *Y*-axis indicates lipid oxidation with reference to known concentrations of MDA. The 150 mg/L demonstrated significantly more lipid oxidation than the control group (*$p<0.05$). Error bars indicate S.E.M.

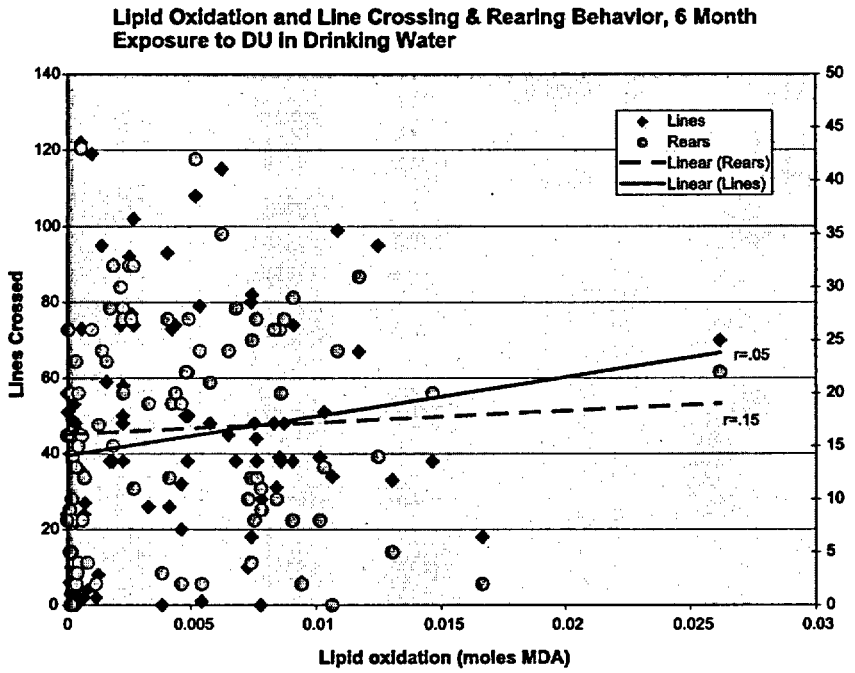

Fig. 11. Correlation and linear regression for brain lipid oxidation levels and rat line crossing and rearing behavior in the open-field. Rearing and line crossing failed to form significant correlations with lipid oxidation levels. Brain lipid oxidation is expressed in terms of known concentrations of the standard MDA.

Lipid oxidation level did not form significant relationships with line crossing or rearing behavior in animals exposed to DU for 6 months ($r(89)$=0.15 and 0.05, respectively, p>0.05; Fig. 11).

4. Discussion

The data indicates that, in the rat, exposure to DU in drinking water for as little as 2 weeks is capable of producing behavioral effects in male rats. These behavioral effects are seen as increased activity in the open-field, in terms of line crossing and rearing. In addition to altered behavior in males, brain lipids in both sexes appear to undergo oxidation that is related to the amount of DU exposure. Brain lipid oxidation also appears to correlate with the number of line crossings and rears seen in the open-field. These behavioral differences and lipid oxidation levels are seen primarily in males exposed to 150 mg/L group, with females and the 75 mg/L group showing only a trend in that direction as exposure times increase.

Increasing the length of DU exposure to 6 months produced similar changes in male line crossing and rearing behavior as was seen in the 2 week exposure groups. However, changes appeared to expand into other behaviors to include bolus deposition, urination, and grooming and to include female rats for some behaviors (urine and bolus deposition and a trend on line crossings). Of particular interest is brain lipid oxidation effects appeared to become less robust and to no longer correlated with behaviors. This suggests that, with increased length of exposure, some type of compensatory mechanism began to reduce the amount and influence of lipid oxidation. However, that compensatory mechanism did not reverse other important effects DU had on the brain, and subsequently, behavioral effects remained and other behaviors were affected.

These findings agree with the larger framework of findings concerning DU. DU is a cumulative toxin, accumulating in bone over time and perhaps magnifying its own effects over time. DU does appear to cross the blood–brain barrier and accumulate in the brain including the hippocampus [16]. Neuronal recordings from the hippocampus in DU-implanted animals demonstrate differences from control animals [24]. Earlier work in this laboratory has found behavioral changes in mice and altered development of mice [2–5]. Work with humans exposed to DU has also demonstrated subtle neuropsychological changes [19], a finding our data supports.

The exact mechanism by which DU may produce behavioral changes is unclear. Lipid oxidation may alter ionic conductance, cell membrane fluidity, or a number of other cellular functions [27]. However, that behavioral changes appear to be more robust even after lipid oxidation no longer correlates with behaviors suggests that other mechanisms are involved. Neuromuscular effects seen after exposure to uranium are probably not due to nephrotoxicity, but rather a direct effect of DU toxicity, possibly due to substitution of calcium in electrophysiologic systems. Effects of DU may vary with the length of exposure or age of the animal. Aging may mask the effects of DU or there may be other compensatory mechanisms [24], a trend noted in this study. It might be worthwhile to investigate the effects of DU on the dopaminergic system. Altered prolactin levels have been seen in Gulf War veterans with embedded

DU fragments [18]. Dopamine is well known to be an inhibitor of prolactin at the hypothalamic–pituitary level.

Lipid oxidation levels for both sexes showed similar dose response curves for both 2 week and 6 months of exposure, yet males seem to be most likely to demonstrate behavioral differences. Differences in gender response to heavy metals and other neurotoxins have been seen in any number of studies. Often, the reasons for the differences are unclear and may be related to gender differences in the pharmacokinetics or pharmacodynamics of toxins. The absolute amount of lipid oxidation is lower in females exposed to similar doses regardless of length of time. Absolute levels of lipid oxidation may be important in altering behavior. It may also be that dissimilar characteristics in sex steroid receptors to the effects of DU may explain the differences seen. Further work will need to be done to determine the reason for the gender differences seen in this study.

The failure to gain weight demonstrated by the 150 mg/L groups suggests that DU exposure has a subtle but pervasive effect on the overall health of the animal, and other physiologic systems are probably affected. We do not believe the failure to gain weight per se affected behavior. Specifically, we did not find any differences in brain weights between any of the groups, either in absolute weights or as a percentage of body weight (data not presented). This included comparing animals exposed for 6 months to those exposed for 2 months. We believe this argues that the failure of animals to gain weight did not effect CNS function. One of the most commonly described toxic effects of uranium is that of nephrotoxicity and it might be argued that the downstream effects of renal impairment by DU indirectly produce behavioral effects. However, data in humans suggest that low-level chronic exposure to DU has no noteworthy nephrotoxicity [19] and was discounted as a significant variable in the effect of DU on hippocampal neurons [24].

Differences in the age of the animals after either 2 weeks or 6 months of exposure is not sufficient to explain differences in brain lipid oxidation. Lipid and protein oxidation is correlated with behavioral changes in senescent animals, typically rats over 24 months of age [7]. The animals used in this study were well below 24 months of age and did not demonstrate senescent behavior. Additionally, assignment of control and experimental groups was age independent eliminating age as a systematic variable.

It is unclear as to what effect DU use on the battlefield may exert a toxic effect on humans. The popular press has focused on any possible DU-related radioactivity and a connection to cancers, often relying on anecdotal evidence. Scientific studies directly addressing the health effects of DU on humans are few. Those studies that have been done using soldiers are limited by the small sample size and heterogeneous nature of the study group. It would be prudent to conduct a larger-scale, environmentally oriented study of local populations and soldiers that would be exposed to DU in dust form.

This study demonstrates that DU is a neuroactive substance in animals and supports the idea that DU may have neurobehavioral effects in humans. Further studies should be performed to look at the neurotoxic potential of DU, especially on developing organisms, which are often much more sensitive to neurotoxins than adult animals.

Acknowledgements

This data was presented in preliminary form at the 6th and 7th Metal Ions in Biology and Medicine Symposium. This work was supported by the Research Services Council of the University of Nebraska at Kearney. Thanks to Mary Burkhart and Brenda Petersen for their assistance in the laboratory.

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The brain is a target organ after acute exposure to depleted uranium

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Abstract

The health effects of depleted uranium (DU) are mainly caused by its chemical toxicity. Although the kidneys are the main target organs for uranium toxicity, uranium can also reach the brain. In this paper, the central effects of acute exposure to DU were studied in relation to health parameters and the sleep–wake cycle of adult rats. Animals were injected intraperitoneally with 144 ± 10 μg DU kg^{-1} as nitrate. Three days after injection, the amounts of uranium in the kidneys represented 2.6 μg of DU g^{-1} of tissue, considered as a sub-nephrotoxic dosage. The central effect of uranium could be seen through a decrease in food intake as early as the first day after exposure and shorter paradoxical sleep 3 days after acute DU exposure (– 18% of controls). With a lower dosage of DU (70 ± 8 μg DU kg^{-1}), no significant effect was observed on the sleep–wake cycle. The present study intends to illustrate the fact that the brain is a target organ, as are the kidneys, after acute exposure to a moderate dosage of DU. The mechanisms by which uranium causes these early neurophysiological perturbations shall be discussed.

Keywords: Depleted uranium; Brain; Paradoxical sleep; Target organ; Kidneys; Toxicity

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To: Evangeline Ngbea
Date: Tue, Jul 25, 2006 6:58 AM
Subject: Fwd: Re: Change of address and status update request

Good morning,

The attached should be docketed as a new comment for PRM- 20-26 (June 15, 2005; 70 FR 34699). Should I print this out, including mentioned sites, and send you a hard copy? How do we usually handle these? Thanks for your help.

Thank you,
Betty
x6863

CC: Frank Cardile

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Creation Date	07/25/2006 6:58:06 AM
From:	Betty Golden
Created By:	BKG2@nrc.gov

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Files	Size	Date & Time
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TEXT.htm	614	
Mail		

Options

Expiration Date:	None
Priority:	Standard
ReplyRequested:	No
Return Notification:	None
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Security:	Standard

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ReplyRequested:	No
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Security:	Standard