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April 21, 2005
AET 05-0020

Mr. Jack R. Strosnider
Director, Office of Nuclear Material Safety and Safeguards
Attention: Document Control Desk
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555-0001

American Centrifuge Plant
Docket Number 70-7004
Submittal of Integrated Safety Analysis Supporting Document

Dear Mr. Strosnider:

Pursuant to a verbal request from the U.S. Nuclear Regulatory Commission (NRC) staff, USEC Inc. (USEC) hereby submits in Enclosure 1 the document listed below that was utilized as input to the American Centrifuge Plant Integrated Safety Analysis.

- K/D-5573, Revision 1, Report on Toxicological Studies Concerning Exposures to UF_6 and UF_6 Hydrolysis Products, R.A. Just, July 1984

If you have any questions regarding this matter, please contact Peter J. Miner at (301) 564-3470.

Sincerely,

M.D. Smith for

Steven A. Toelle
Director, Nuclear Regulatory Affairs

cc: Y. Faraz, NRC HQ
B. Smith, NRC HQ

Enclosures: As Stated

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Enclosure 1 to AET 05-0020

Submittal of Integrated Safety Analysis Supporting Document

MARTIN MARIETTA

K/D-5573
Revision 1

REPORT ON TOXICOLOGICAL STUDIES CONCERNING EXPOSURES TO UF_6 AND UF_6 HYDROLYSIS PRODUCTS

R. A. Just

INFORMATION CONTAINED WITHIN
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Richard A. Covell
4/14/05

JULY 1984

This document has been approved for release to the public by:
D.S. Napolitan 7/19/04
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MANAGED BY
MARTIN MARIETTA ENERGY SYSTEMS, INC.
FOR THE UNITED STATES
DEPARTMENT OF ENERGY

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K/D-5573
Revision 1

REPORT ON TOXICOLOGICAL STUDIES CONCERNING EXPOSURES TO UF_6 AND UF_6 HYDROLYSIS PRODUCTS

R. A. Just

Sponsor: E. O. Sternberg

Date of Issue - July 1984

Oak Ridge Gaseous Diffusion Plant
Oak Ridge, Tennessee 37831
operated by
Martin Marietta Energy Systems, Inc.
for the
U.S. DEPARTMENT OF ENERGY
under Contract No. DE-AC05-840R21400

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1. Introduction

In the fall of 1979, the Department of Energy indicated that the accident analysis section of safety analysis reports should provide information about the toxicological effect of uranium hexafluoride (UF_6) releases on off-site and on-site personnel. This report describes the activities leading to recommendations for exposure/consequence relations to be used in safety analysis reports. These recommendations apply only for this very specific use of characterizing the effects of acute accidental exposures. The results are not intended to be used to set or modify established uranium exposure guidelines.

Uranyl fluoride (UO_2F_2) and hydrogen fluoride (HF) result from the hydrolysis of UF_6 with atmospheric moisture. Both UF_6 and UO_2F_2 are soluble in water; consequently, toxicity data for HF and soluble uranium are necessary to assess the consequences of a postulated UF_6 release. So, the Union Carbide Corporation—Nuclear Division (UCC-ND), Engineering's Safety Analysis Group entered into short-term consulting contracts with a group of experts in the field of chemical toxicity of soluble uranium and HF. The group included the following toxicologists.

Dr. J. B. Hursh
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University of Rochester

Dr. L. J. Leach
Department of Radiation Biology & Biophysics
University of Rochester

Dr. P. E. Morrow
Department of Radiation Biology & Biophysics
University of Rochester

Dr. F. S. Smith
Department of Radiation Biology & Biophysics
University of Rochester

Dr. M. E. Wrenn
Radiobiology Division
Department of Pharmacology
School of Medicine
University of Utah

In the fall of 1979, they were asked to apply known data and make their best judgments about the toxicological effects of postulated exposures to soluble uranium and HF. This information became the basis for the development of interim Design and Analysis Guidelines for estimating the toxicity of soluble uranium and HF.

To improve the accuracy of the Design and Analysis Guidelines, a exposure-response database was established for estimating human health hazards associated with acute exposures to hydrolyzed UF_6. The data were compiled from a series of toxicity experiments (on rats and guinea pigs) initiated in 1982 at the University of Rochester, under the direction of Leach. The scope of this investigation included the development of toxicity data needed to assess the consequences of acute exposures to UF_6 and UF_6 hydrolysis products similar to the exposures that have been postulated during preparation of the gaseous diffusion plant safety analysis reports.

After the experimental work was completed in late 1983, a "Delphi" panel of toxicologists was formed to interpret the experimental results. UCC-ND asked the toxicologists who had participated in the 1980 investigation to reexamine their initial toxicity estimates in light of the new experimental data.[1,2,3] Hursh, Leach, Morrow, and Wrenn agreed to develop revised toxicity estimates; because of other commitments, Smith could not participate.

2. Method of Approach

At the request of UCC-ND, each of the toxicologists agreed to develop completely independent estimates of uranium and HF toxicity. They were asked to present preliminary estimates of the toxicity of these UF_6 hydrolysis products at a December 8, 1983 "Delphi" meeting. At this meeting, the toxicologists discussed their approaches for estimating toxicity. The toxicologists were then asked to reevaluate their toxicity estimates, if necessary as a result of the discussions, and to submit documentation describing the rationale used in developing their "final" estimates. Appendix A contains unedited copies of their reports. The toxicologists have reviewed a draft copy of this report, and they indicated that they agreed with the described approach for evaluating the toxicity of uranium and HF.

3. Estimates of Uranium Toxicity

The four toxicologists used different approaches in developing their estimates of the toxicity of soluble uranium. Leach used data from his rat and guinea pig experiments to correlate absorbed-dose levels (mg-U/kg body weight) and concentration-time products to a predicted human health effect. Hursh, Morrow, and Wrenn used Leach's animal data and other applicable information to develop an absorbed-dose level corresponding to a predicted human health effect and to calculate a concentration-time product. The airborne concentration and duration of exposure at which dose, D_e (mg-U/kg), would be delivered are given by

$$C = mD_e/Itf ,$$

where

C = airborne uranium concentration, mg-U/m^3,

I = respiration rate, m^3/min,

t = exposure time, min,

m = body mass of reference human, kg, and

f = fraction of inhaled uranium absorbed by the body.

Hursh, Morrow, and Wrenn assumed

1. an International Commission on Radiological Protection (ICRP) reference body weight of 70 kg,
2. an ICRP light activity respiration rate of 20 L/min (0.02 m^3/min), and
3. an ICRP resting respiration rate of 7.5 L/min (0.075 m^3/min).

Morrow and Wrenn also assumed that 43% (f = 0.43) of the inhaled uranium would be absorbed by the body. Hursh assumed that 50% (f = 0.5) of the inhaled uranium would be absorbed.

As noted previously, Leach used his experimental animal data to relate directly the absorbed dose of uranium to the airborne concentration; however, applying the above equation to Leach's data is informative. If the reference human weighs 70 kg, Leach's data would indicate that the product of the respiration rate and the fraction of uranium retained, I*f, is approximately 3.2 L/min. This value is approximately 60% of the value calculated when assuming a 7.5-L/min respiration rate and an f value of 0.43. This leads to the conclusion that either

1. the assumed value of f (0.43) is too large, or
2. the respiration rate (7.5 L/min) has been overestimated, or
3. both quantities have been overestimated.

In a January 4, 1984, discussion with R. A. Just, Leach indicated that his toxicity estimates should be considered as being based on a resting respiration rate of 7.5 L/min; he agreed that the estimates could be extrapolated to a light activity respiration rate (20 L/min) by multiplying the concentration-time products stated in his report by 7.5/20 or 0.38. Leach also indicated that his estimates could be applied over a range of exposure times of 2 to 60 min and that his estimates should be conservative for exposure times of 0.5 to 2 min.

Table 1 is a summary of the four estimates of uranium toxicity. The exposure levels shown in the table are based on a resting respiration rate of 7.5 L/min. If toxicity estimates are required for a light activity respiration rate, the tabulated exposure levels should be multiplied by 0.38.

An examination of Table 1 shows that different nomenclature was used to characterize sublethal health effects. The following sections contain a rationale for interpreting and implementing the four different estimates of uranium toxicity.

3.1 Estimates of Lethal Exposure Level

As shown in Table 1, Morrow used a 10% reduction from the ≤10-min exposure level in developing exposure levels for 30- and 60-min exposures, while the other three toxicologists predicted a constant exposure level independent of the exposure time. It seems reasonable to neglect Morrow's 10% reduction for 30- and 60-min exposures, thereby resulting in the following summary of 50% lethality estimates (estimates of LD50):

Toxicologist	Basis (mg-U/kg)	Exposure Level for 50% Lethality ($mg\text{-}U/m^3$) (min)
Hursh	2	37,333
Leach	2.5	92,167
Morrow	1	20,000
Wrenn	1	22,000
Average	1.63	42,875
Range of Estimates	1 to 2.5	20,000 to 92,167

Table 1. Summary of Estimates of Uranium Toxicity

Toxicologist	Health Effect	Basis[a] (mg-U/kg)	Exposure Level[b] (mg-U/m^3)(min)	Exposure Time (min)
J. B. Hursh	50% Lethality	2	37,333	
	Reversible Injury	0.07	1,307	
	Maximum No Effect Exposure	0.054	1,008	
L. J. Leach	50% Lethality	2.5	92,167	
	10% Lethality	1.0	35,683	
	0.1% Lethality	0.15	5,375	
	Renal Injury	0.040	1,375	
	No Effect	0.015	550	
P. E. Morrow	50% Lethality	1.0	20,000	≤ 10
			18,000	30
			18,000	60
	Injury	0.05	1,000	≤ 10
			900	30
			600	60
	No Effect	0.01	200	≤ 10
			180	30
			120	60
M. E. Wrenn	50% Lethality	1.0	22,000	
	Permanent Damage	0.3	6,500	
	Onset of Damage	0.07	1,500	
	No Observable Effect in Man	0.04	870	

[a]Absorbed quantity of uranium per kg of body weight. As stated in the report, the toxicologists used different methodologies in predicting the exposure level (mg-U/m^3)(min) corresponding to an absorbed quantity of uranium (mg-U/kg).

[b]Exposure level is defined as the product of the airborne concentration and the exposure time. Based on an ICRP resting respiration rate of 7.5 L/min.

As stated previously, Morrow and Wrenn used the standard ICRP methodology for calculating the 50% lethal exposure level (given the absorbed dose in mg-U/kg), Leach used his experimental data to establish this relationship, and Hursh used a minor modification of the ICRP methodology. Based on discussions with the ORGDP and GAT industrial hygiene staffs, it was concluded that the ICRP methodology should be used to relate the absorbed quantity of uranium (mg-U/kg) to the inhaled exposure. Therefore, the ICRP methodology should be used to establish the 50% lethal exposure level based on the average absorbed dose of 1.63 mg-U/kg. The 50% lethal exposure level then is:

$$\text{50\% lethal exposure level} = \frac{(1.63\ \text{mg-U/kg})(70\ \text{kg})}{(0.43)(7.5\ \text{L/min})(0.001\ \text{m}^3/\text{L})}$$

$$= 35{,}380\ (\text{mg-U/m}^3)(\text{min}) .$$

<u>Therefore, it is recommended that, for purposes of safety analysis consequence evaluation, an exposure level of 35,000 (mg-U/m^3)(min) should be considered 50% lethal for exposure durations less than 30 minutes.</u> Use of the ICRP methodology results in a lower, more conservative estimate of the lethal exposure level than that obtained by averaging the four concentration-time products.

Leach's lethality estimates include exposure levels predicted to result in 10% and 0.1% lethality. However, as Leach has indicated in discussions with R. A. Just, the predicted exposure levels corresponding to 10% and 0.1% lethality are not as precise as the

estimate of the 50% lethal level. After consultation with his statistician, Leach concluded that his estimate of the 10% lethal exposure level was a statistically valid estimate and that the 0.1% lethal exposure level was significantly more uncertain. Morrow agreed that the 10% lethal exposure level could be estimated with a reasonable level of certainty. Leach estimated that 10% lethality would result from an absorbed quantity of uranium equal to 40% (1/2.5) of the quantity of uranium which corresponds to the 50% lethal level. The 50% lethal level is the value used in the DOE-ORO uranium enrichment facilities safety analysis applications. The 10% lethal level, 14,000 (mg-U/m^3)(min), may be more appropriate for other applications such as for emergency preparedness planning. It should be noted that the 50% lethal level, LD50, is the value usually used in risk evaluations to characterize a possible lethal exposure level. Therefore, the 50% lethal level may be sufficient for most safety analysis applications.

According to Morrow, estimations of 0.1% lethality "... is statistically impractical without a hundred-fold increase in the number of animals tested . . ." Therefore, in the absence of sufficient data to predict reliably the 0.1% lethal exposure level, it is recommended that the 0.1% lethal estimate <u>should not</u> be used in safety analysis consequence evaluations.

3.2 Estimates of Renal Injury Exposure Level

The four toxicologists used different nomenclature in describing a health effect corresponding to Renal Injury (see Table 2); however, "Reversible Injury," "Renal Injury," "Injury," and "Onset of Damage" are all viewed as corresponding to renal injury. Therefore, the estimates of renal injury are as follows.

Using the average value of 0.058 mg-U/kg, the ICRP methodology yields the following:

$$\text{Renal Injury Exposure} = \frac{(0.058\ \text{mg-U/kg})(70\ \text{kg})}{(0.43)(7.5\ \text{L/min})(0.001\ \text{m}^3/\text{L})}$$

$$= 1259\ (\text{mg-U/m}^3)(\text{min})\ .$$

It is recommended that, for purposes of safety analysis consequence evaluation, an exposure level of 1250 $(\text{mg-U/m}^3)(\text{min})$ should be considered as producing renal injury for exposure times less than 30 min, and (0.6) (1250) = 750 $(\text{mg-U/m}^3)(\text{min})$ should be considered as the renal injury exposure level for 60-min exposures. Linear interpolation should be used for exposure times between 30 and 60 min.

Although Morrow was the only toxicologist to provide time-dependent exposure level (product of the airborne concentration and the exposure time) estimates, the use of his 60% reduction factor for 60-min exposures seems prudent. In a discussion with R. A. Just, Morrow indicated that using linear interpolation between 30 and 60-min would be appropriate. The relatively small 10% reduction

Table 2. Summary of Estimates of Renal Injury Exposure Level

Toxicologist	Health Effect	Basis (mg-U/kg)	Exposure Level (mg-U/m^3)(min)	Exposure Time (min)
Hursh	Reversible Injury	0.07	1,307	
Leach	Renal Injury	0.04	1,375	
Morrow	Injury	0.05	1,000	$\leq$ 10
			900	30
			600	60
Wrenn	Onset of Damage	0.07	1,500	
Average		0.058	1,296[a]	
Range of Estimates		0.04 to 0.07	1,000 to 1,500[a]	

[a]Obtained using Morrow's estimates for a 10-min exposure time.

provided by Morrow for the 30-min exposure level has been neglected.

3.3 Estimates of No Effect Exposure Level

Table 3 shows the exposure levels estimated to result in no effect. Using the average value of 0.03 mg-U/kg, the ICRP methodology yields the following:

$$\text{Maximum No Effect Exposure Level} = \frac{(0.03\ \text{mg-U/kg})(70\ \text{kg})}{(0.430)(7.5\ \text{L/min})(0.001\ \text{m}^3/\text{L})}$$

$$= 651\ (\text{mg-U/m}^3)(\text{min})\ .$$

For purposes of safety analysis consequence evaluation, it is recommended that an exposure level of 650 $(\text{mg-U/m}^3)(\text{min})$ should be considered the maximum "No Effect" exposure level for exposure times less than 30 min, and $(0.6)(650) = 390\ (\text{mg-U/m}^3)(\text{min})$ should be used for 60-min exposures. Linear interpolation should be used for exposure times between 30 and 60 min.

3.4 Implementation of Uranium Toxicity Recommendations

Figure 1 shows the recommended estimates of soluble uranium toxicity. As noted on the figure, four health effect levels have been established: No Effect, Mild Health Effects, Renal Injury, and Lethal. The Mild Health Effects regime corresponds to exposure levels that may result in observable short-term biological effects, but these exposure effects would not, in themselves, result in either a short- or long-term impairment in the body's ability to function.

Table 3. Summary of Estimates of No Effect Exposure Level

Toxicologist	Basis (mg-U/kg)	Exposure Level (mg-U/m^3)(min)	Exposure Time (min)
Hursh	0.054	1008	
Leach	0.015	550	
Morrow	0.01	200	$\leq$ 10
		180	30
		120	60
Wrenn	0.04	870	
Average	0.03	657[a]	
Range of Estimates	0.01 to 0.054	200 to 1008[a]	

[a]Obtained using Morrow's estimate for a 10-min exposure time.

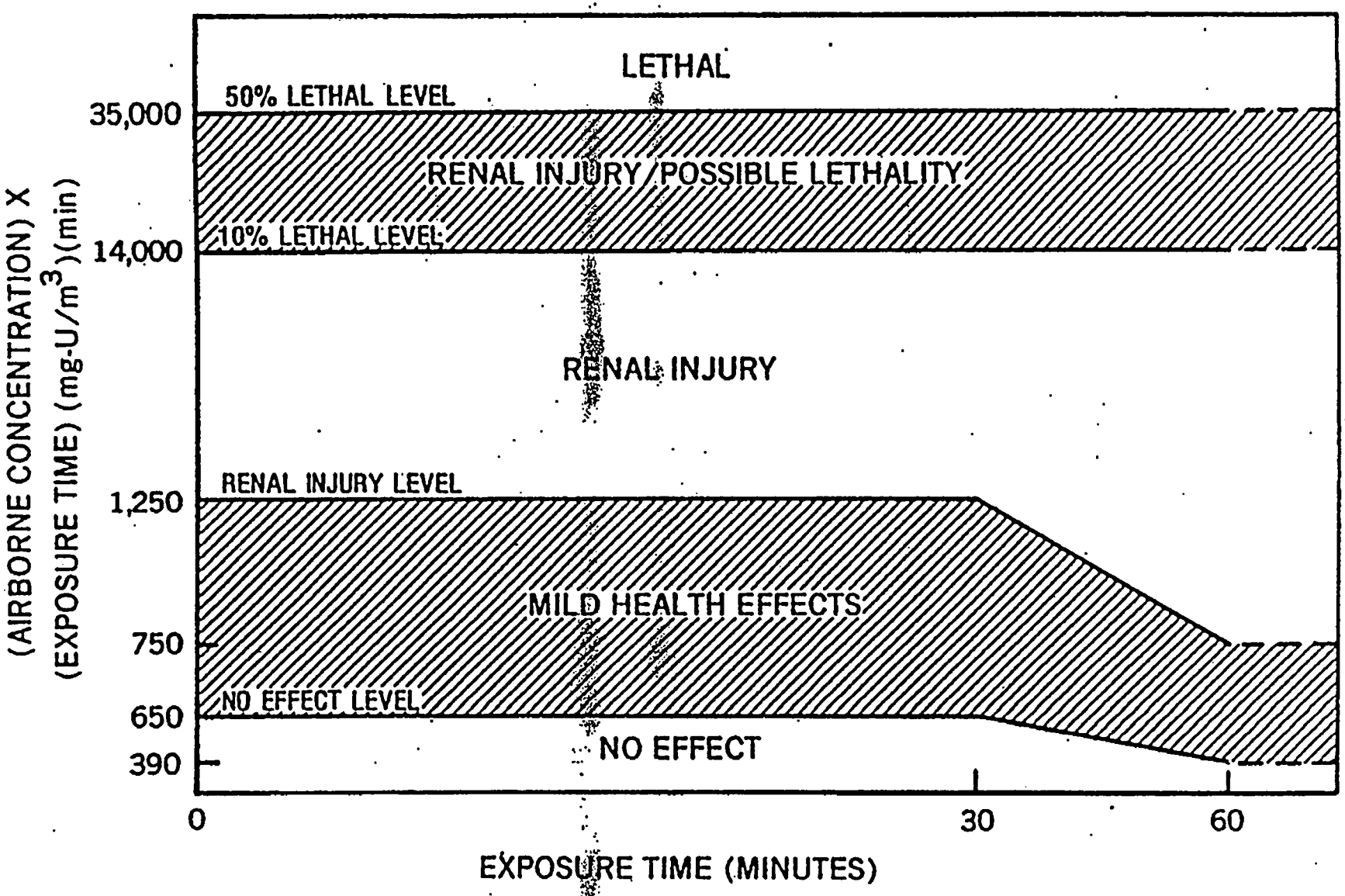

Figure 1
Toxicity of Acute Exposures to Soluble Uranium

The toxicologists were asked to estimate uranium toxicity for exposure times of 0.5 to 60 min. Therefore, estimates of uranium toxicity for exposure times greater than 60 min should be based on the 60-min toxicity estimates.

4. Estimates of the Toxicity of Hydrogen Fluoride

Available estimates of HF toxicity include estimates from Wrenn as well as guidance provided by the Occupational Safety and Health Administration (OSHA), the National Institute for Safety and Health (NIOSH), and the National Research Council. Table 4 summarizes available HF toxicity data.

4.1 Estimates of the Lethal Concentration Level

Wrenn estimated that an inhaled exposure of 53,000 (mg-HF/m^3)(min) would be lethal for exposure times of 0.5 to 60-min. It is recommended that, for purposes of safety analysis consequence evaluation, an inhaled exposure of 53,000 (mg-HF/m^3)(min) be considered lethal.

4.2 Estimates of the Irritation Concentration Level

As noted in Table 2, Dr. Wrenn estimated that an HF concentration of 26 mg-HF/m^3 would only result in irritation for any exposure time. The NIOSH/OSHA 30-min "Immediately Dangerous to Life or Health" level and the National Research Council's 10-min emergency

Table 4. Summary of Estimates of Hydrogen Fluoride Toxicity

Source	Effect	Concentration ($mg\text{-}HF/m^3$)	Exposure Time (min)
(see Section 4.3)	Detection by Smell	0.02 to 1	—
National Institute for Occupational Safety and Health (NIOSH)	Short-Term Exposure Limit (STEL)	5	15
NIOSH	Threshold Limit Value (TLV)	2.5	480
Occupational Safety and Health Administration (OSHA)	Permissible Exposure Limit (PEL)	2	480
National Research Council	Emergency Exposure Limit	13.3	10
NIOSH/OSHA	Immediately Dangerous to Life or Health (IDLH)	13.3	30
M. E. Wrenn	No Effect	2.6	Indefinite
	Irritation	26	Indefinite
	Lethal[a]	105,000	0.5
		26,000	2
		10,500	5
		5,250	10
		877	60

[a]Wrenn's HF lethality estimates are based on an inhaled exposure level of 53,000 ($mg\text{-}HF/m^3$)(min).

exposure limit is approximately 13.3 mg-HF/m^3. Therefore, it is recommended that, for purposes of safety analysis consequence evaluation, an HF concentration of 26 mg-HF/m^3 should be considered for exposure times of 0 to 10 min; and an HF concentration of 13.3 mg-HF/m^3 for exposure times greater than 10 min should be considered as the "Irritation Level".

4.3 Estimates of the Odor Threshold

The NIOSH criteria document for occupational exposures to HF cites two Russian reports that indicate an HF odor threshold of 0.02 to 0.04 mg-HF/m^3.[4,5] However, a third report indicates that the HF odor threshold is approximately 1 mg-HF/m^3.[6] It is recommended that, for purposes of safety analysis consequence evaluation, an HF concentration of 1 mg-HF/m^3 should be considered "Detectable by Smell".

4.4 Implementation of Hydrogen Fluoride Toxicity Recommendations

The recommended estimates of HF toxicity are presented in Fig. 2. As noted on the figure, five health effect levels have been established: No Effect, Smell/No Health Effects, Smell/Possible Irritation, Irritation/Possible Health Effects, and Lethal. Estimates of HF lethality should be based on an inhaled exposure level (airborne concentration * exposure time) of 53,000 (mg-HF/m^3)(min).

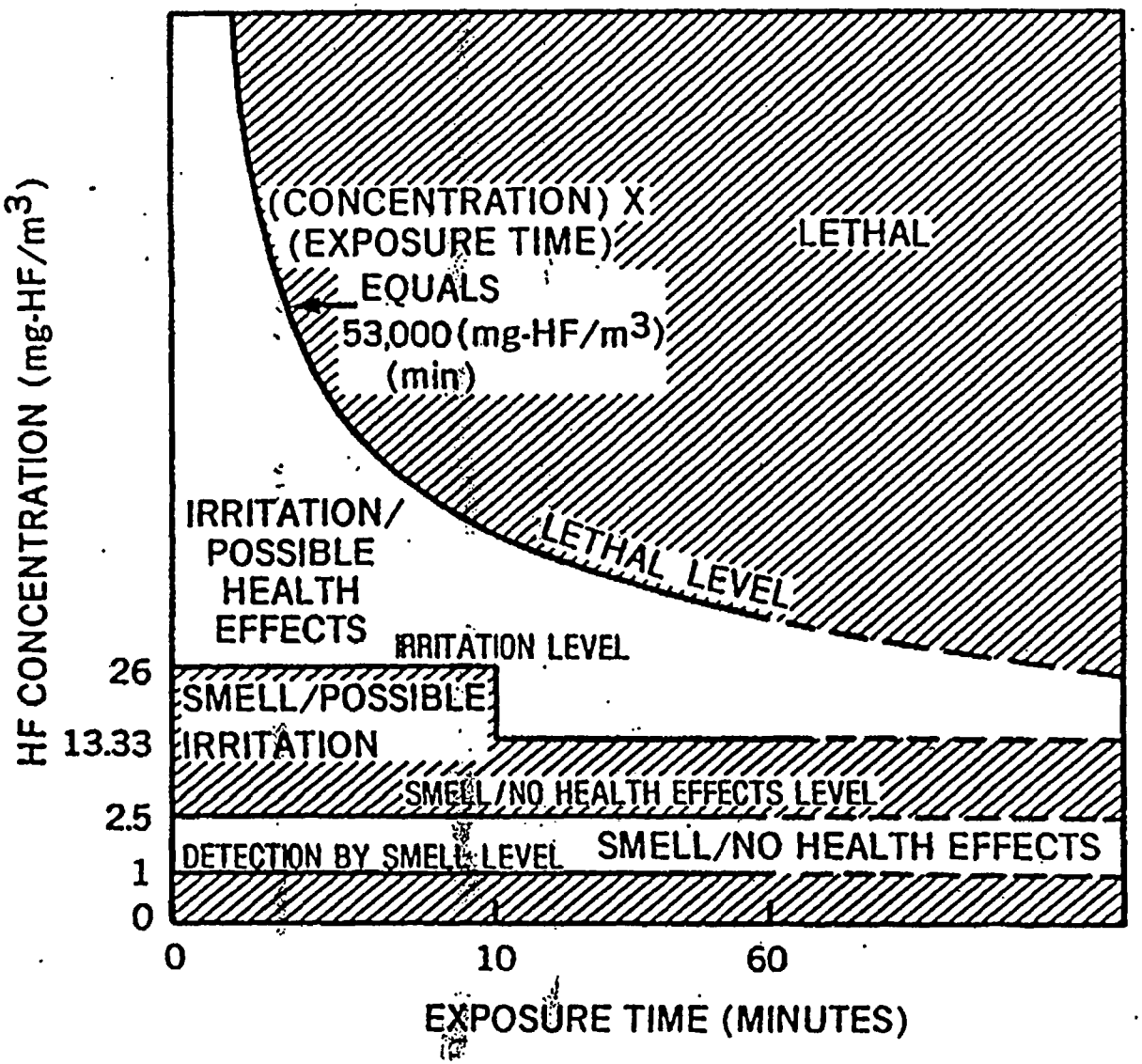

Figure 2
Toxicity of Acute Exposures to Hydrogen Fluoride

5.0 Use of Information in Safety Analysis Reports

The data and recommendations presented herein do not attempt to account for the many variables that must be addressed in accident evaluations for safety analysis reports. These variables include, but are not limited to, ability of personnel to escape quickly, physical activity level at time of exposure, variation in the spatial concentration of the U and HF, and protective breathing apparatus worn by workers. These all must be considered when using the exposure level/consequence recommendations if a proper risk evaluation is to be made in the safety analysis report.

6. References

1. Acute Effect of Inhalation Exposure to Uranium Hexafluoride and Patterns of Disposition UF_6 UO_2F_2 Studies in Experimental Animals, Report Period: June 1978 - July 1979, NUREG/CR-1045, August 1980.

2. Metabolic Rate and Evaluation of Injury in Rats and Dogs Following Exposure to the Hydrolysis Products of Uranium Hexafluoride (Implications for a Bioassay Program Related to Potential Releases of Uranium Hexafluoirde, Report Period: July 1979 - October 1981, NUREG/CR-2268/RH, December 1982.

3. L. J. Leach, Gelein, et. al., A Final Report on the Acute Toxicity of the Hydrolysis Products of Uranium Hexafluoride (UF_6) When Inhaled by the Rat and Guinea Pig, K/SUB/81-9039/3, Martin Marietta Energy Systems, Inc., April 1984.

4. M. S. Sadilova, "Material for Standardization of the Maximum Permissible Concentration of Hydrogen Fluoride in the Air of Populated Areas," Biol. Deistvie Gig Znach Atmos Zagryaz 10:186-201, 1967 (USSR).

5. Z. Y. Lindberg, "The Combined Effect of Hydrogen Fluoride and Sulfur Dioxide on the Body of Man and Animals," Biol. Deistvie Gig Znach Atmos. Zagryaz 11:32-43, 1968 (USSR).

6. W. Thomas, "Environmental Impact of a Potential UF_6-Release Resulting from an Accident in a UO_2 Fabricating Plant", Gesellschaft fur Reaktorsicherheit mbH Garching, 1979, (Federal Republic of Germany).

Appendix A

Reports by the Toxicologists

Dr. J. B. Hursh
Department of Radiation Biology & Biophysics
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John B. Horst
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Pittsford, NY 14534

20 December, 1983

Some changes have been made in the estimates provided 4 years ago relating degrees of biological effect to the amounts of uranium hexafluoride acutely inhaled by exposed humans. These changes and a table of related exposure times and air uranium concentrations are submitted below. On following pages please find notes which supplement the notes supplied earlier in the light of the experimental work conducted in the interim, reports of which we were requested to review. May I note that as before I have not supplied estimates for hydogen fluoride inasmuch as I have no special competence in that area.

.....

ACUTE LUNG INTAKES

	December 1979	December 1983
	mg U	mg U
No effect(Maximum)	5	7.5
Discomfort (Minimum)	any concentrations greater than 10 mg U/liter	
Onset of health effect	7.2	10
LD_{50} -30 days	100	280

No intakes resulting in permanent physiological injury were estimated because of insufficient biological evidence.

MATRIX LISTING ESTIMATED URANIUM CONCENTRATIONS IN AIR SUFFICIENT TO PRODUCE BIOLOGICAL EFFECTS AS NOTED WHEN THE EXPOSURE WAS FOR STIPULATED SHORT TIMES.

Exposure time in minutes**	No effect max. conc. mg/liter	Irritation*	Repairable injury min. conc. mg/liter	LD_{50} mg/liter
0.5	1.5		2	56
2	.38		.50	14
10	.075		.10	2.8
30	.025		.033	.93
60	.0125		.0167	.47

* I estimate that irritation occurs at all time periods if the concentration exceeds 10 mg U/liter.

** I have assumed a minute volume of 10 liters.

SUPPLEMENTARY NOTES - DECEMBER 1983

These notes are to be considered as a supplementary update of the material supplied in December 1979. They are intended to justify the selections of the estimates given on pages 1 and 2 of this report and to make known my position on the five questions raised by the experimental material reviewed.

1. In view of the dog and rat data (NUREG/CR-2069, NUREG/CR-1045) should the estimate of the threshold for repairable injury to the kidney of man be changed? The animal data show 0.1 mg U/kg for rats and 0.02 mg U/kg for dogs as the minimal dose which causes reversible kidney injury. The data from the Rochester experiment of man (1) indicates that patients 3, 4, 5, and 6 received intravenous doses of 0.016, 0.030, 0.042, and 0.071 mg U per kilogram in that order. Only patient 4 showed minimal signs of kidney injury in response to their battery of tests. A total of 13 workers (7-11) exposed to accidental releases of UF_6 sustained absorbed doses of from 1.3 to 4.0 mg U/kg. In none of these cases was albumin found in the urine. Subsequent medical examinations were all negative. Using these data as a guide, I have selected 0.07 mg/kg as a reasonable value for men, intermediate between the dog and the rat. The reference man (70 kg) would on this basis reach the reversible injury threshold when he had inhaled 10 mg U equivalent to 5 mg U absorbed into the body.

2. What is the effect of the first injury-producing dose of UF_6? Can complete recovery occur? Is tolerance induced? NUREG/CR-2268 questions the belief that injury to the kidney can be completely repaired. The biochemical tests return to normal at different rates post exposure but the implication of the data is that given time all the tests show normal

function. However, histological evidence of changed cell structure and persistent injury (at 60 days) is cited, as well as more extensive injury when a second dose was administered at 60 days and specimen were collected 60 days later. The key to the question may be the definition of "physiological recovery." I believe that there is a dosage range that produces injury from which recovery occurs in the sense that there is no clinical evidence of functional impairment. There is abundant word of mouth evidence of industrial exposures, return to work and no subsequent history of kidney failure. Separate surveys by Howland, Butterworth, and Lippman attest to this (1).

NUREG/CR-2268 finds no evidence of tolerance to low level injury effects after tracheal instillation of UO_2F_2 when a second dose was delivered 60 days after the first.

3. Should special consideration be given to aerosol size in the specification of uranium air concentrations required to produce the specified biological effects at chosen exposure times? If the July 1978 ICRP lung model is used, it may be found that for our purposes 50% absorbtion is approximately correct for MMADs from 0.2 to 5.0 microns. As reported by L. J. Leach, Gelein et al., 1983, ("The Biological Effects of Hydrolyzed Uranium Hexafluoride (UF_6) when Inhaled by the Rat and Guineas Pig," to be issued) particle size rarely exceeded this upper limit.

4. Can the added effect of HF be disregarded and limits set only on the basis of uranium-produced potential injury? It would appear that, although some differences exist between the effects of HF as reported in the literature and in experimental work under review, the answer is in the affirmative.

5. Do the results of the experiments reported by L. J. Leach, et al., mandate an increase in the estimate of the LD_{50} for man? A related question is: Do these data discredit the premise that dose can be expressed as the product of uranium concentration in the air times minutes of exposure independent of the exposure time span? Please refer to Fig. 1 (attached) which plots calculated minute volumes for rats versus concentration of uranium in the air breathed. Leach's experiments PD, 1C, 2C, 8A, 9B, and 7A provided the data which were used in the following equation,

$$\text{ml/min} = \frac{\text{inhaled mg U/min}}{\text{mg U/liter air}} \times 1000 .$$

From this figure it is very clear that the high LD_{50} - 2 min of 34 mg/kg is simply a consequence of the rats holding their breath. The tabular data supplies only 2 points for the curve in Fig. 1, marked as 7A (4 ml/min) at 80 g U/cubic meter and 8A (18 ml) at 0.95 g U/cubic meter. The points responsible for the ascending portion of the LD_{50} - 2-min curve are associated with concentrations in excess of 30 g U/cubic meter and according to the Fig. 1 curve would relate to minute volumes less than 9 ml. The 10-min exposure data provide an LD_{50} estimate of 17 mg U/kg and only 2 points on the rising phase of the graph are associated with concentrations greater than 15 g/cubic meter. It is likely that the normal minute volume for the rat is nearer to 56 ml which was the average of 6 rats exposed for 60 min and is the point PD on the Fig. 1 graph.

Supposing that the above interpretation is valid, what can we learn from the experiments? I do not believe that in setting up prospective accident situations it is prudent to assume that man would behave exactly

like a rat. For one thing rats have a much more sensitive sense of smell and it is safe to assume that either U or HF has been detected with the resultant reduced air intake rate. The ability of the worker to hold his breath or to breathe sparingly may be a safety factor, but it can play no part in the prospective accident scenario. It is clear that additional LD_{50} experiments need to be done using exposure times of 20 and 30 min.

Inasmuch as

1. use of the 2-min series which applied to man would specify 2.4 g inhaled (1.2 g absorbed) would be ill-advised;
2. the "educated guesses" (December 1979) suggested 1 mg/kg equivalent to 0.14 g inhaled (0.070 g absorbed). This is a factor of 17 times lower.
3. based on the 10-min rat series, the LD_{50} for man would be 1.2 g inhaled (0.60 g absorbed);
4. the educated guesses are based on very little hard evidence and the LD_{50} (10-min rat series) if multiplied by 0.3 might approximate normal breathing results, yielding an estimate for man of 0.36 g U inhaled as a rat based LD_{50}.

I have settled on an intermediate estimate of 0.28 g U inhaled (0.14 g absorbed) as producing an LD_{50} - 30 days for man.

Figure 1 is also my basis for a guess that irritation may develop at uranium air concentrations greater than 10 g/cubic meter.

John B. Hursh

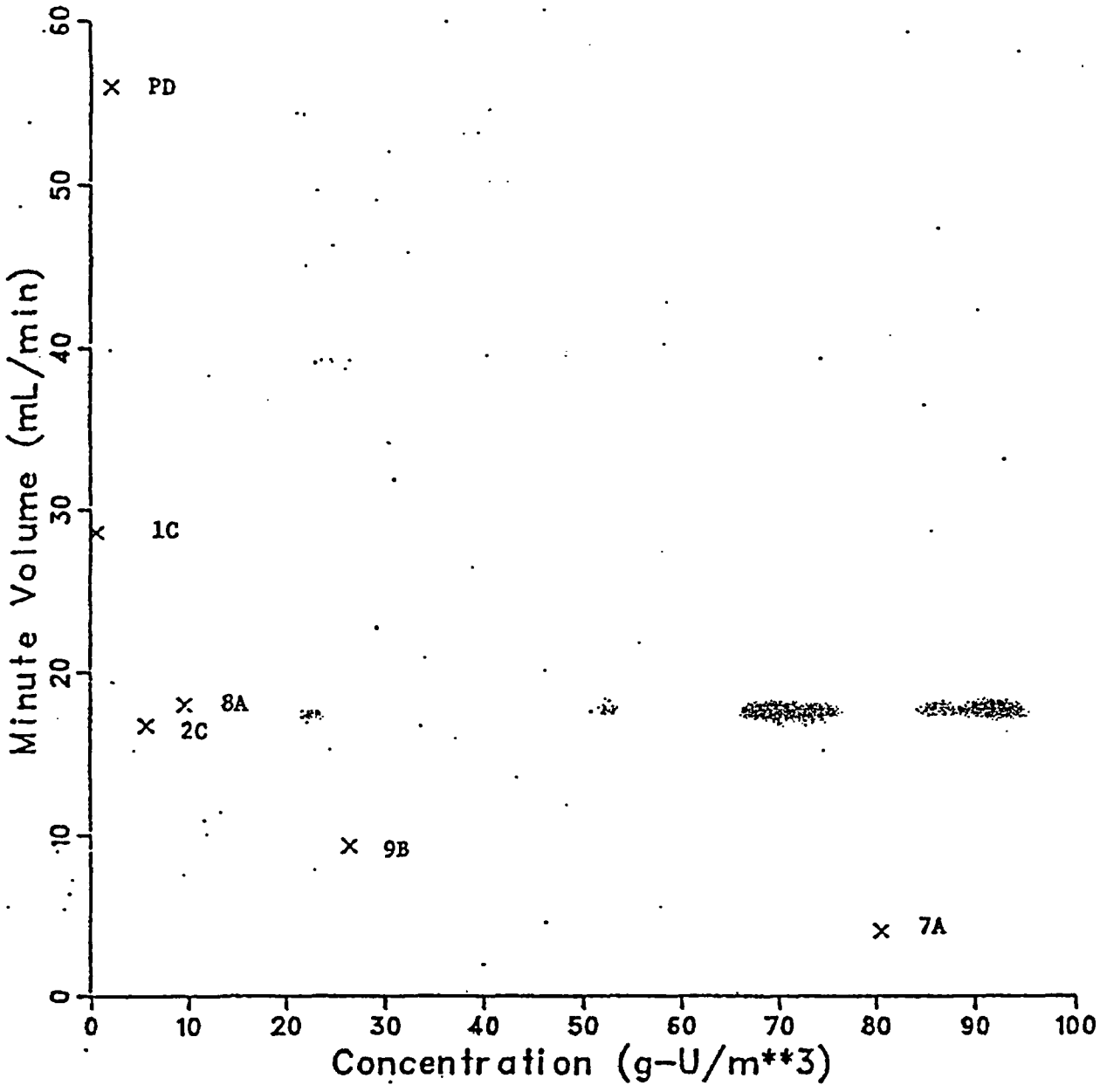

Fig. 1. Data from L. J. Leach's Lethal Dose Experiments

John B.Hursh
34 Woodland Road
Fittsford,N.Y.
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17 December,1979

Explanatory Notes

1. I have provided estimates for the UF_6 matrix only,inasmuch as I am not qualified to predict effects from exposure to HF.
2. It is implicit that chemical injury to the kidney is the governing criterion and that,for the range of enrichment postulated, and for the same exposure to UF_6 the radiological injury is substantially less.
3. In filling in the matrix I have relied primarily on the guidance provided by reports of accidental exposures of workers to UF_6 releases. The data available in June 1972 have been collected in Table 4.9 ,pg 221 ,reference (1). To these data may be added the report of an accident occurring 1 July 1977 (2). In the interpretation of these data it must be appreciated that estimates of intake depend on the measurements of urinary excretion of uranium. It is possible to make reliable stipulations of the amount that entered the blood,because carefully controlled intravenous injections of man have been performed and show that an average 72% of the soluble uranium injected appeared in the first 24-hour urine(3,4). In order to infer the lung input from the blood input, it is customary to use a lung model. Generally speaking,early accident reports used the old ICRP-NCRP lung model(5) which postulates that 25% of the soluble uranium inhaled would be transported to the blood. A newer, more specific and more detailed model has been presented by the Lung Model Task Group. In a slightly modified form it is described in reference (6). Using this improved model ,assigning the uranium aerosol to Class D transportability and assuming that the AMAD of the particles = 0.2 μm, stipulates that altogether 54% of the uranium inhaled passes into the blood. This distinction in the manipulation of urinary data has been taken into consideration in deriving the limits on lung intake.
4. Inasmuch as the kidney is designated as the critical organ it makes no difference whether the exposure time is 30 seconds or eight hours. The reason for this is that the lung clearance half-time is short (equal or less than 2.5 - 6 hours,(7)) compared to loss from the kidney equal to 15 days (1) and therefore the maximum concentration produced in the kidney is the same for present purposes. Consequently the next step in filling out the matrix was to develope lung intake ranges(regardless of exposure times) which would fit the effect categories.
5. The "no effect" limit on intake emerges clearly from the accident data and in my judgement may be set at 0-5mg. lung intake. The upper limit selected is reenforced by consideration of the intervenous injection series carried out at University of Rochester and at Oak Ridge (1). Basset et al found a threshold for transient kidney damage at at 3.9 mg. uranium intervenous (equivalent to 7.2 mg. lung intake). Luessenhop et al (Oak Ridge study) estimate borderline kidney damage at 0.1mg per kg.body weight(equivalent to about 14 mg. lung intake for a reference man at 70 kg. body weight.

J.B.H.

6. The accident accounts and intravenous studies formed the basis for selection of a range of lung intake which would bring about completely repairable kidney damage. This range is designated as 5-15 mg. uranium.

7. I found great difficulty in in finding any data which would define an intake which would produce transient physical discomfort. It is true that Howlands account (1) describes three seriously injured cases which were "unusually nervous and apprehensive" but these individuals suffered repairable kidney damage as well.

I find equal difficulty in designating inputs which would produce "permanent physiological damage" and "permanent disability". It is true that animal studies have revealed neoplasms and widespread fibrosis (1) but this study involved an inhalation period of 5 years and the lung effects were produced by insoluble uranium particles. I know of no way to extrapolate to acute accidents involving soluble uranium. Indeed it is my opinion that these effects could not be produced by short exposures to soluble uranium. Hodge. in his thorough-going review of the literature (1) quotes the doses used by many investigators to produce experimental nephritis. in animals. Consideration of the doses used suggests that many would be lethal to man.

Finally it is of interest that disregarding these effect categories creates only 7. holes in my response to the matrix.

8. The selection of the threshold for a lethal effect in man can not be firmly based on accident data. Howland's account (1) reports the death of 2 men but the dose is not well defined and the presence of excess steam associated with the production of HF complicates the interpretation. The insufflation experiments using soluble uranium introduced into the lungs of rabbits come nearest to providing a guidepost. With injected amounts as little as 5 mg. (per 3 kg rabbit.) 53% were dead in 28 days(8). Additional animal data may be found in the literature review by Hodge(see Chapter 1 ,reference (1)) Selected data from this source yields the information that from 0.35 -- 2 mg/kg was found to be a lethal dose in a variety of animals. Luessenhop(4) estimates the lethal dose for man at 1 mg. /kg. body weight. Ericsson et al (9) estimate the lethal dose for man at 1 mg./kg. basing their choice on animal data with a range of lethal doses from "0.1 mg.U/kg of body weight to 20 mgU/kg of body weight.". Thomas (10) states that "Based on the ICRF lung model ,150 mg of soluble uranium may be lethal if inhaled". It should be noted that approximately half this amount would enter the blood. The fact that all of these sources agree in choosing about 1mg/kg of body weight as the lethal dose should not be unduly regarded as inspiring confidence in the result. All estimates are based on the same inadequate experimental data.

The value that I have chosen as lethal is a lung intake equal or greater than 100 mg U. in the form of a soluble compound. This implies a transfer to the blood of about 50 mg U.

9. It may be that a maximum of toxicity occurs as the concentration of uranium is increased through the range specified in the matrix. One can imagine a concentration so great that little if any of the uranium would be respired. I do not have experience in this area and if such an aggregation and precipitation of uranium particles does occur my response would need to be modified . As specified in an earlier section, I have assumed deposition in the lung to occur as specified in the Task Group Lung Model.

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A FINAL REPORT

TOXICOLOGIC ASSESSMENTS OF ACUTE EXPOSURES TO HYDROLYZED URANIUM HEXAFLUORIDE

by

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January 1984

TOXICOLOGIC ASSESSMENTS OF ACUTE EXPOSURES TO HYDROLYZED URANIUM HEXAFLUORIDE

I. INTRODUCTION

As part of an ongoing analysis of existing and planned uranium (U) enrichment facilities, Union Carbide Corporation, Nuclear Division (UCC-ND) is assessing the human health consequences of postulated uranium hexafluoride (UF_6) accidental discharges. UF_6 and its hydrolysis products UO_2F_2 and HF are chemically reactive and toxic, therefore it seemed prudent that we more fully understand the health effects associated with these toxicants.

After reviewing the scientific literature, it was clear there is a paucity of knowledge concerning the human health hazards posed by exposure to UF_6, UO_2F_2 and HF from accidental releases of UF_6.

Therefore, the main objective of our recent work (Leach, Gelein et al., 1983) was to collect toxicologic information from new animal studies (primarily with rats), to establish a dose-response data base for estimating human health hazards associated with acute exposures to hydrolyzed UF_6. These studies are briefly summarized in the first part of the report that follows.

II. EXPERIMENTAL

Forty-six single exposures of ten rats each, and 13 exposures of six guinea pigs each, conducted for two, five or ten minutes duration at air concentration levels ranging from 0.44 g U/m^3 + 0.16 g HF/m^3 to 276.67 g U/m^3 + 94.07 g HF/m^3, were carried out in a nose-only

exposure unit designed specifically to handle the hydrolysis products of UF_6. Survivors of each exposure were individually housed in metabolism cages where they were observed for 14 consecutive days for signs of U and HF intoxication. On the 14th day postexposure, selected rats were humanly killed, necropsied and samples of major organs were reserved for histopathologic study and U analyses. When enriched UF_6 (94 percent ^{235}U) was used, the urine and feces from each animal were measured daily for U content by gamma counting. Selected samples of urine were bioassayed in order to trace the course of renal injury during the two week postexposure period.

III. HIGHLIGHTS OF EXPERIMENTAL FINDINGS

A. The quantitative relationship between the air concentration of UO_2F_2 (an aerosol) and HF (a gas), in the exposure chamber was in good agreement with theoretical values predicted by the hydrolysis equation $UF_6 + 2H_2O \rightarrow UO_2F_2 + 4\ HF$. This is demonstrated graphically in Figure 1, where the HF concentration (g/m^3) is plotted against UO_2F_2 concentration (g/m^3). The dotted line is the theoretical regression curve derived from the hydrolysis equation listed above, and defines the equivalent ratio of UO_2F_2 : HF as 1 : 0.26. The solid line is the regression curve obtained from evaluating the air concentration data in all of the studies in which we had analytical values for HF (39 out of 46). The regression equation based on our experimental data is: $\log HF = -0.341 + 0.867 \log UO_2F_2$ ($R_2 = 0.91$).

This may be compared to the theoretical regression equation which is $\log HF = -0.587 + \log UO_2F_2$.

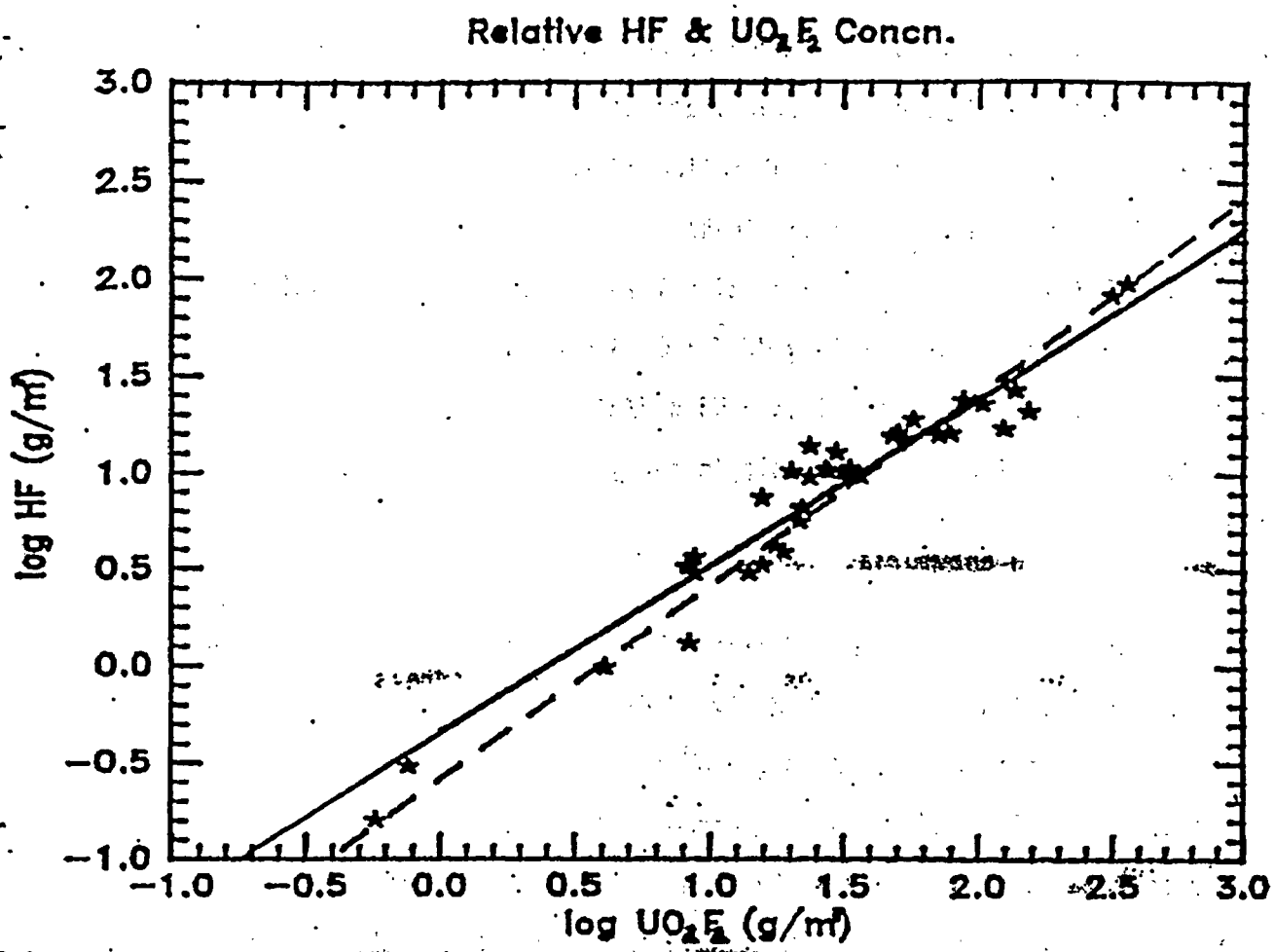

FIGURE 1. THE RELATIONSHIP BETWEEN THE AIR CONCENTRATION OF UO_2F_2 AND HF IN THE EXPOSURE CHAMBER. THE REGRESSION EQUATIONS ARE SHOWN BELOW.

THEORETICAL - - - - - - - - - $\log HF = -0.587 + \log UO_2F_2$

EXPERIMENTAL ———— $\log HF = -0.341 + 0.867 \log UO_2F_2$

B. Since there was little evidence of HF toxicity in surviving animals examined 14 days postexposure, attention was focused on the clearly demonstrated toxic chemical action of the U component (UO_2F_2) of hydrolyzed UF_6. Urine bioassays indicated mild to severe renal injury at all concentration levels and exposure durations tested, except the lowest (0.44 g U/m^3 + 0.16 g HF/m^3) two minute exposure of rats. Rats exposed at 0.55 g U/m^3 + 0.24 g HF/m^3 for five minutes exhibited mild morphologic changes in renal tubules, glucosuria and enzymuria.

C. Histopathologic studies indicated that the kidneys of rats exposed at all concentration levels of hydrolyzed UF_6, except the two lowest in the two minute exposures (0.44 g U/m^3 + 0.16 g HF/m^3 and 2.18 g U/m^3 + 0.71 HF/m^3) showed evidence of the classical renal injury associated with $^{+6}$U toxicity when examined 14 days after exposure. The lungs of surviving rats, examined 14 days postexposure, showed no histopathologic changes that could be attributed to the inhalation of UO_2F_2 and HF. However, some of the animals that died during exposure and shortly thereafter, showed congestion, acute inflammation and focal epithelial degeneration in the upper respiratory passages. The tracheas, bronchi and lungs showed acute inflammation with epithelial degeneration, acute bronchial inflammation and acute pulmonary edema and inflammation, respectively. These changes in the respiratory tract may be due to the inhalation of HF but the severity was judged to be rarely life-threatening (except at the extremely high exposure levels) and would not change the overall mortality picture in

these studies except for the predisposing a few animals to a somewhat earlier death.

D. Presented in Figure 2 are dose (air concentration of U in g/m^3) vs. response (probability of death) curves for two, five, ten and 60* minute rat studies along with the general equation and specific values for a and b which reproduce each curve. It should be noted that the slopes of these curves are very steep between 0.10 and 0.90 probability of death, indicating that for a small change in air concentration of U a large change in the predicted mortality will occur.

E. Summarized in Table 1. are selected exposure data including biostatistical evaluations of the dose-mortality information. If attention is focused on the last column in the lower portion of the table it can be seen that the CT products of the two and ten minute rat studies differ significantly, indicating that the product of air concentration of U in g/m^3 (C) X exposure time in minutes (T) does not have a constant value for a given biological effect (in this case LC50).

F. Dose-mortality curves for two minute rat and guinea pig studies are compared graphically in Figure 3. These curves indicated that the rat is two, four and 20 times more resistant to hydrolyzed UF_6 than the guinea pig at the corresponding LC50, LC10 and LC0.1 points on the curves. This difference in species susceptibility is not an uncommon

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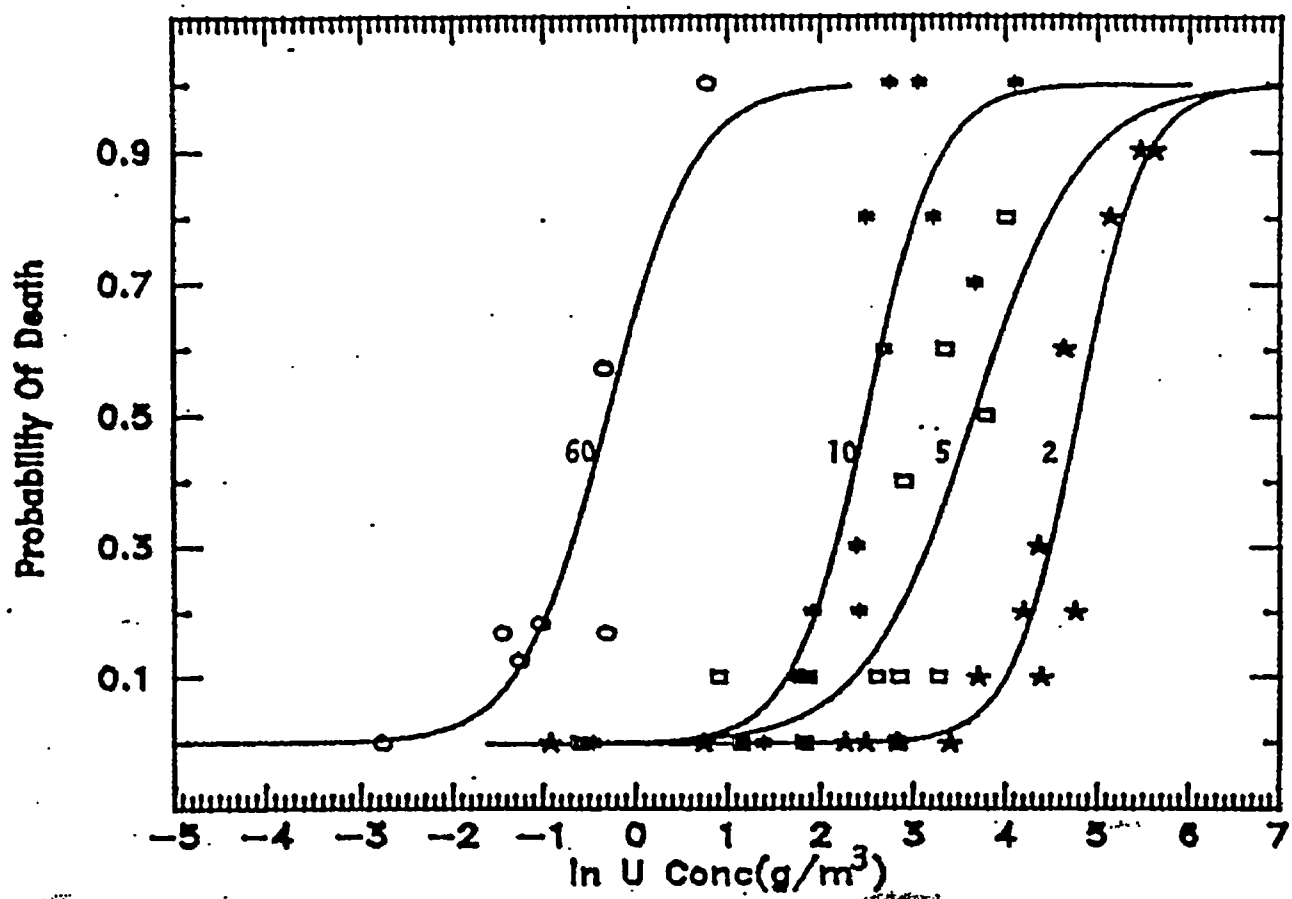
* These data were taken primarily from other sources (Morrow et al., NUREG/CR-2268).



$$P = 1 / 1 + e^{-(a + b \ln U)}$$

ANIMAL SPECIES	EXPOSURE TIME (minutes)	VALUES FOR a	b
RAT	2	13.450	- 2.808
RAT	5	6.182	- 1.692
RAT	10	6.460	- 2.599
RAT	60	- 0.656	-2.150

FIGURE 2. DOSE (AIR CONCENTRATION OF U IN g/m^3) VS RESPONSE (PROBABILITY OF DEATH) CURVES FOR 2, 5, 10 AND 60 MINUTE RAT STUDIES.

TABLE 1. SELECTED DATA TAKEN FROM THE UNPUBLISHED REPORT OF LEACH, GELEIN et al, 1983

NO. AND SPECIES	NO. OF EXPERIMENTS	EXPOSURE DURATION (min)	DOSE (Air Concn in g U/m^3) VS RESPONSE (% Mortality) BIOSTATISTICS				
			$LC50_{14\ da}$	SDEV	95% CONF. INTER.	$LC10_{14\ da}$	95% CONF. INTER.
150 RATS	15	2	120	11.5	99.3 - 146	55.0	40.0 - 76.0
170 RATS	17	5	38.6	7.08	26.8 - 55.7	10.5	6.48 - 17.1
140 RATS	14	10	12.0	1.04	10.1 - 14.3	5.16	3.65 - 7.29
51 RATS	7	60	0.74	0.15	0.49 - 1.10	0.27	0.12 - 0.47
78 G. PIGS	13	2	62.1	11.12	43.4 - 88.8	13.5	5.45 - 33.5

(Table Continued)

AIR CONCN IN g U/m^3 VS % MORTALITY BIOSTATISTICS		PRODUCT OF THE $LC50_{14\ da}$(C) AND EXPOSURE TIME (T)		
$LC0.1_{14\ da}$	95% CONF. INTER.	C (g U/m^3)	T (min)	C·T (g U/m^3·min)
10.3	4.13 - 25.6	120	2	240*
0.65	0.12 - 3.68	38.6	5	193
0.84	0.32 - 2.20	12.0	10	120*
0.03	0.004 - 0.18	0.74	60	44
0.51	0.03 - 8.88	62.1	2	124

* THESE NUMBERS ARE STATISTICALLY DIFFERENT AND INDICATE THAT IN THE RAT STUDIES THE CT PRODUCT DOES NOT HAVE A CONSTANT VALUE FOR A GIVEN BIOLOGIC RESPONSE (PERCENT MORTALITY).

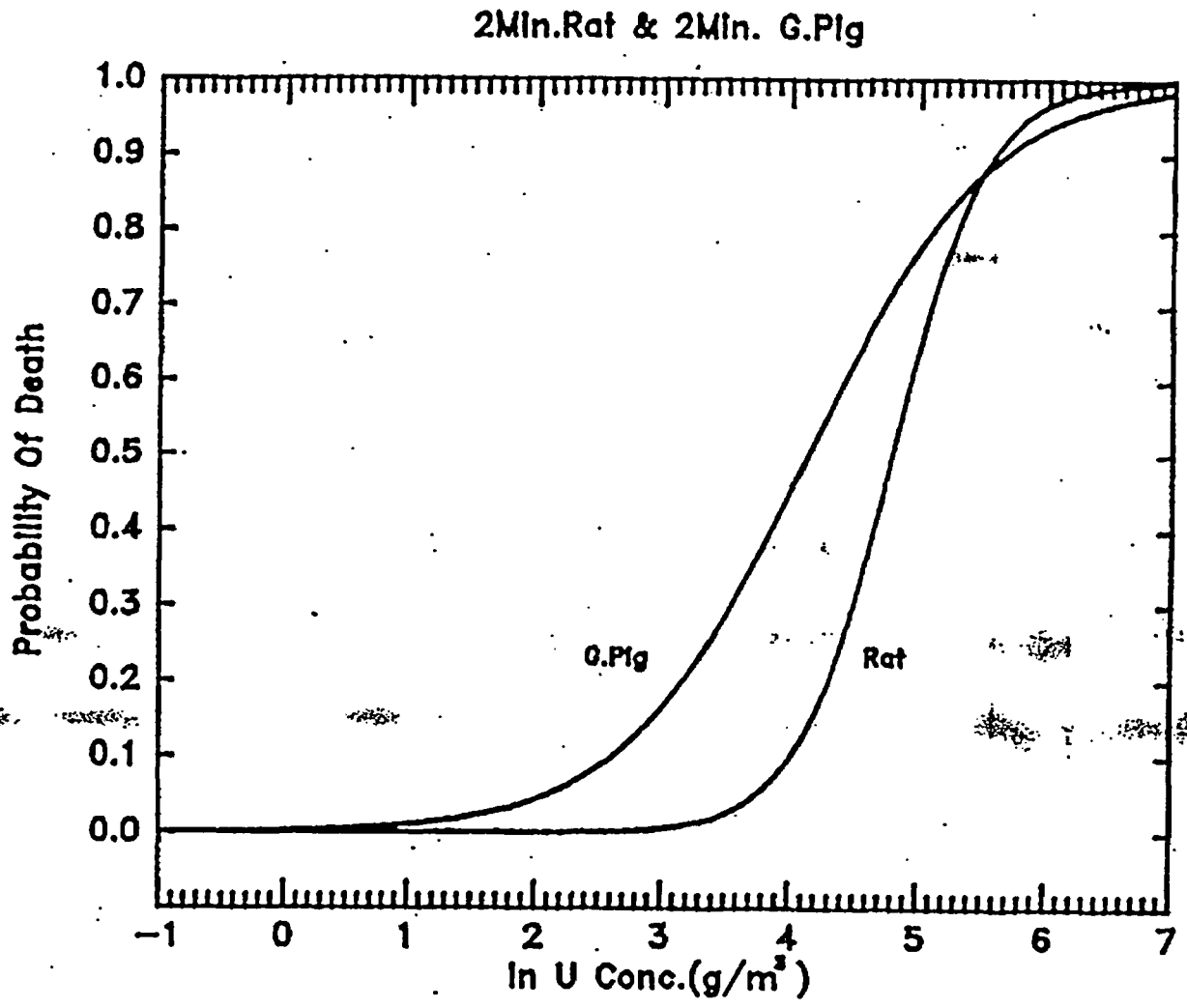


FIGURE 3. A COMPARISON OF THE DOSE-RESPONSE CURVES FOR RAT AND GUINEA PIG EXPOSED TO THE HYDROLYSIS PRODUCTS OF UF_6 FOR TWO MINUTES

finding in toxicology and should be examined in greater depth in order to more accurately predict the position of man on the mammalian sensitivity scale under the unique exposure conditions of UF_6 accidental discharges.

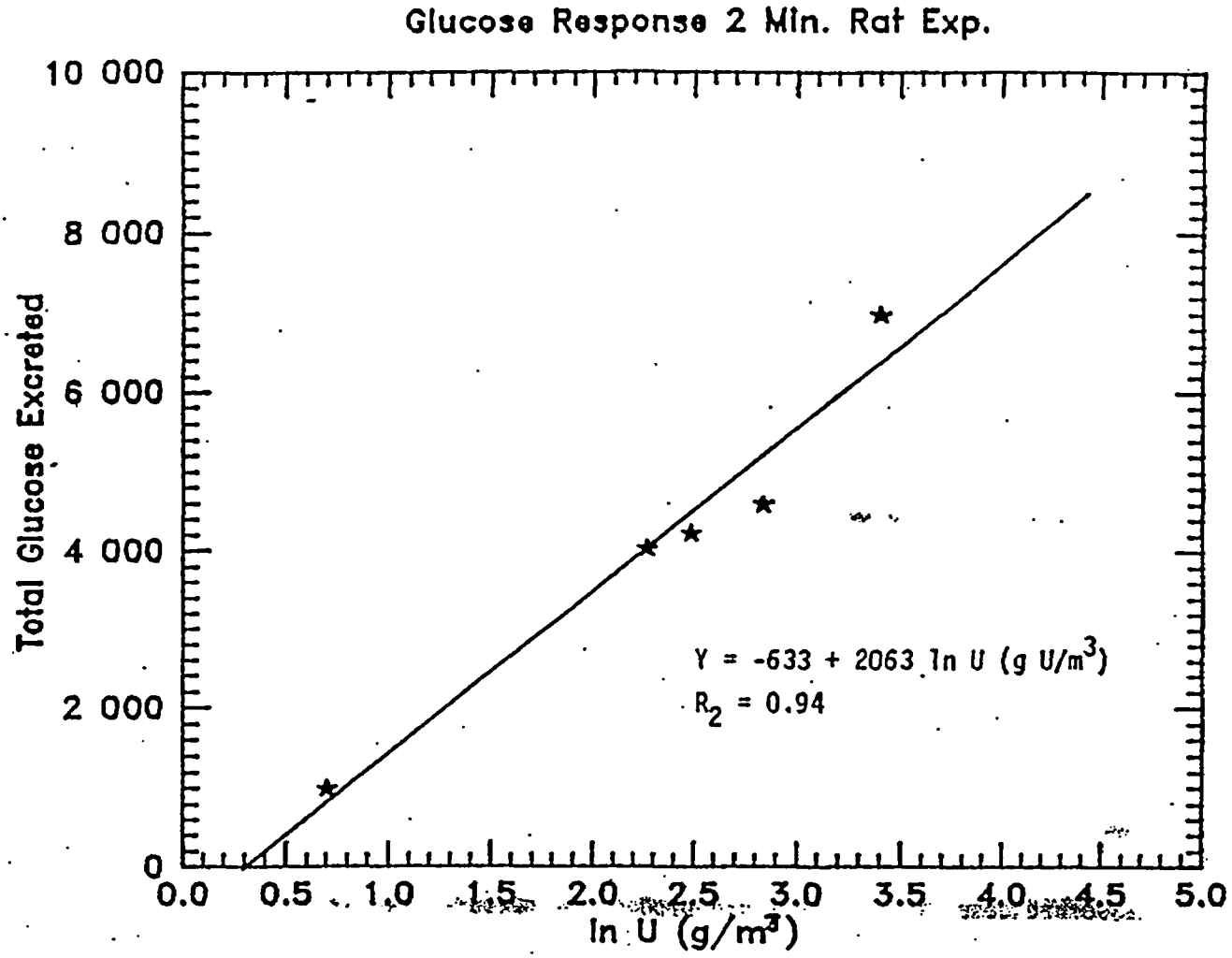
G. In our new animal studies glucosuria was the most sensitive indicator of renal injury associated with exposure to ^{+6}U. Using the rat data, an attempt was made to determine the highest dose of airborne U that produced no decernable elevation in glucose excreted in the urine. In Figure 4 glucose excretion in μm (minus the control value) is plotted against the ln of the air concentration of U in g/m^3. As shown in the figure, the number obtained was 1.36 g U/m^3 for a two minute exposure to the hydrolysis products of UF_6.

H. In a similar manner as above, we tried to estimate the highest absorbed dose of U which would produce no measureable elevation in urinary glucose. In Figure 5, total glucose excretion is graphed against the ln of the absorbed dose of U in mg/kg. The value obtained equaled 0.024 mg U/kg.

IV. DOSE RESPONSE ESTIMATES FOR THE RAT USING OUR NEW ANIMAL DATA (Leach, Gelein et al., 1983).

A. Dose-response estimates for rats exposed to the hydrolysis products of UF_6 for two, five or ten minutes duration are given in Table 2. Included in the table are predicted biologic effects ranging from $LC50_{14\ da}$ to a "no ill effects" level. Corresponding absorbed

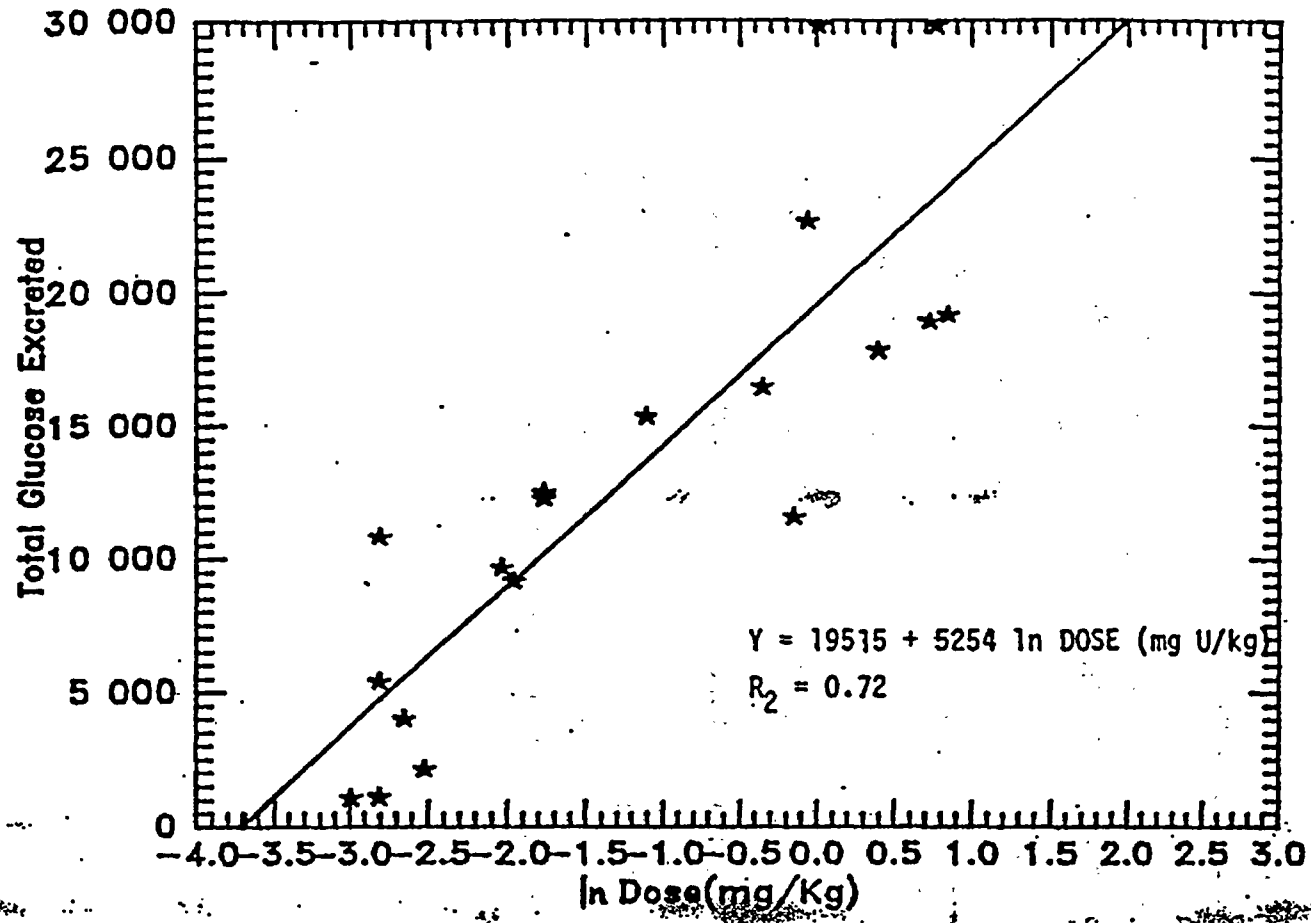
GLUCOSE EXCRETION VS AIR CONCENTRATION OF U IN SELECTED STUDIES WITH RATS EXPOSED TO THE HYDROLYSIS PRODUCTS OF URANIUM HEXAFLUORIDE FOR 2 MINUTES



HIGHEST ESTIMATED AIR CONCENTRATION OF U PRODUCING NO ELEVATION IN GLUCOSE EXCRETION = 1.36 g U/m^3

FIGURE 4. GLUCOSE EXCRETION IN μm PLOTTED AGAINST THE ln OF THE AIR CONCENTRATION OF U IN g/m^3

TOTAL GLUCOSE EXCRETION VS ABSORBED DOSE OF U IN RATS EXPOSED FOR TWO MINUTES TO THE HYDROLYSIS PRODUCTS OF URANIUM (U) HEXAFLUORIDE (UF_6)



TOTAL GLUCOSE EXCRETED = TOTAL GLUCOSE EXCRETED DURING 9 POSTEXPOSURE DAYS - 585 μM GLUCOSE (CONTROL VALUE)*

* 585 μM GLUCOSE = 65 μM GLUCOSE/DAY X 9 DAYS

HIGHEST ESTIMATED ABSORBED DOSE PRODUCING NO ELEVATION IN GLUCOSE EXCRETION = 0.024 mg U/kg

FIGURE 5. GLUCOSE EXCRETION IN μm PLOTTED AGAINST THE ln OF THE ABSORBED DOSE OF U IN mg/kg

TABLE 2. DOSE-RESPONSE ESTIMATES FOR RATS EXPOSED TO THE HYDROLYSIS PRODUCTS OF URANIUM HEXAFLUORIDE FOR TWO, FIVE OR TEN MINUTES (Based on data taken from the report of Leach et al, 1984).

PREDICTED EFFECTS	MEAN AND RANGE OF ABSORBED DOSES (mg U/kg BODY WT.)			MEAN AND RANGE OF CT PRODUCTS* IN 95% CONFIDENCE INTERVAL (mg U/m^3·minutes)		
	LOW	MEAN	HIGH	LOW	MEAN	HIGH
$LC50_{14\ da}$	3.75	5.00	6.25	144,500	184,333	237,800
$LC10_{14\ da}$	1.50	2.00	2.50	49,600	71,367	103,500
$LC0.1_{14\ da}$	0.23	0.30	0.36	4,020	10,750	30,530
RENAL INJURY (NON-LETHAL)	0.060	0.080	0.100	2,260	2,750	3,540
"NO ILL EFFECTS"			0.030			1,100

* CT IS THE PRODUCT OF THE AIR CONCENTRATION IN mg U/m^3 (C) AND EXPOSURE TIME IN MINUTES (T)

doses of U were estimated by close inspection of the rat experiments utilizing 94 percent ^{235}U enriched UF_6. The numbers in the columns in which the low and high values for the 95 percent confidence intervals of the LC50, LC10, and LC0.1 were calculated by averaging the corresponding confidence values and multiplying by the respective exposure times of two, five or ten minutes (data obtained from Table 1). These low and high values provide a range of CT products associated with the predicted effects and corresponding absorbed doses of U.

B. A dose-response matrix for rats exposed to hydrolyzed UF_6 is pictured in Figure 6. Here the predicted biologic effects, shown in Table 2, are recorded on the matrix and can be equated to air concentration of U and HF and exposure times from one to ten minutes. It should be noted that the interfaces between biologic effects are not precisely defined in this matrix.

V. DOSE-RESPONSE ESTIMATES FOR MAN

A. In our new animal studies we went to great lengths to closely mimic the extraordinary exposure conditions caused by accidental releases of UF_6 which produce extremely high airborne concentrations of UO_2F_2 and HF (sometimes exceeding 100s of g/m^3). The older animal data from the 1950s (Voegtlin and Hodge) and the very limited human information fully discussed by Hursh, Morrow and Wrenn at ORNL on December 8, 1983, do not reflect these unique exposure conditions or in the case of the human data refer to the specific toxicants in question. I therefore take the position that our new animal work (that reflected

FIGURE 6. RAT DOSE-RESPONSE MATRIX FOR EXPOSURES TO THE HYDROLYSIS PRODUCTS OF NATURAL URANIUM HEXAFLUORIDE (UF_6)

(Predicted Primarily From The Unpublished Animal Data of Leach, Gelein et al, 1983)

$$UF_6 + 2H_2O \rightarrow UO_2F_2 + 4HF$$

	HF (mg/m^3)	34×10^{-4}	34×10^{-3}	34×10^{-2}	34×10^{-1}	34×10^{0}	34×10^{1}	34×10^{2}	34×10^{3}	34×10^{4}	34×10^{5}	34×10^{6}	34×10^{7}	34×10^{8}
	U (mg /m^3)	1×10^{-2}	1×10^{-1}	1×10^{0}	1×10^{1}	1×10^{2}	1×10^{3}	1×10^{4}	1×10^{5}	1×10^{6}	1×10^{7}	1×10^{8}	1×10^{9}	1×10^{10}
MINUTES	0													
	1	S	S	S	S	S	S	L.1 + I	L50 + I	L	L	L	L	L
	2	S	S	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L
	3	S	S	S	S	S	I	L.1 + I	L	L	L	L	L	L
	4	S	S	S	S	S	L.1 + I	L.1 + I	L	L	L	L	L	L
	5	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
	6	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
	7	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
	8	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
	9	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
	10	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L

L = LETHAL TO MORE THAN 50% OF THOSE EXPOSED

L50 = LETHAL TO 50% OF THOSE EXPOSED

L10 = LETHAL TO 10% OF THOSE EXPOSED

L.1 = LETHAL TO 0.1% OF THOSE EXPOSED

S = "NO ILL EFFECTS"

I = INJURY (PRIMARILY NON-LETHAL RENAL)

exposure conditions closer to the real-life situation) be used as a framework for predicting human health hazards associated with acute exposures to hydrolyzed UF_6 until more pertinent data becomes available. Since our limited guinea pig data suggests a two-fold sensitivity difference between this species and the rat, I would suggest that a safety factor of two be employed when extrapolating our rat data to man. This, I believe, would put our predictions for rats in good agreement with Hursh's, Morrow's and Wrenn's predictions for man up to the point where exposure may be lethal. Here, the divergence of opinion is hinged primarily on definitions of degree of lethality. Since there are no human data to anchor these points, I would use the rat data with an applied safety factor of 2. See Table 3.

B. Presented in Figure 7 is my version of a dose-response matrix applicable to man. It should be readily apparent that the matrix is the same as that for the rat, except a safety factor of 2 has been applied to the CT products (see Table 3). This is a somewhat different approach than the one I presented at the December 1983 Meeting where I used a sliding scale safety factor of from 12 to 30. While the sliding scale is more conservative and probably justifiable, a safety factor of 2 across the board seems to be sufficient at this time.

C. The information in Table 3. can also be summarized in graphical form as shown in Figure 8. Here the predicted health effects in humans, listed on the vertical axis, are plotted against the ln of 2 dose parameters (1) the estimated absorbed dose of U in mg/kg of body weight (see upper scale on horizontal axis) and (2) the CT product of air concentration of U in mg/m^3 (C) and exposure time in minutes (T).

TABLE 3. DOSE-RESPONSE ESTIMATES FOR MAN ACUTELY EXPOSED TO THE HYDROLYSIS PRODUCTS OF URANIUM HEXAFLUORIDE (Based primarily on adjusted animal data taken from the report of Leach et al, 1984).

PREDICTED EFFECTS	CRITERIA USED IN PREDICTIONS	MEAN AND RANGE OF ABSORBED DOSES (mg U/kg BODY WT.)			MEAN AND RANGE OF CT PRODUCTS* (mg U/m^3·minutes)		
		LOW	MEAN	HIGH	LOW	MEAN	HIGH
$LC50_{14\ da}$	RAT DATA/2	1.56	2.50	3.32	56,744	92,167	120,572
$LC10_{14\ da}$	RAT DATA/2	0.47	1.00	1.56	17,287	35,683	56,744
$LC0.1_{14\ da}$	RAT DATA/2	0.08	0.15	0.47	2,952	5,375	17,287
RENAL INJURY (NON-LETHAL)	RAT DATA/2	0.015	0.040	0.080	550	1,375	2,952
"NO ILL EFFECTS"	RAT DATA/2			0.015			550

* CT IS THE PRODUCT OF THE AIR CONCENTRATION IN mg U/m^3 (C) AND EXPOSURE TIME IN MINUTES (T)

FIGURE 7. MAN DOSE-RESPONSE MATRIX FOR EXPOSURES TO THE HYDROLYSIS PRODUCTS OF NATURAL URANIUM HEXAFLUORIDE (UF_6)
(Predicted Primarily From The Unpublished Animal Data of Leach, Gelein et al, 1983)

$$UF_6 + 2H_2O \longrightarrow UO_2F_2 + 4HF$$

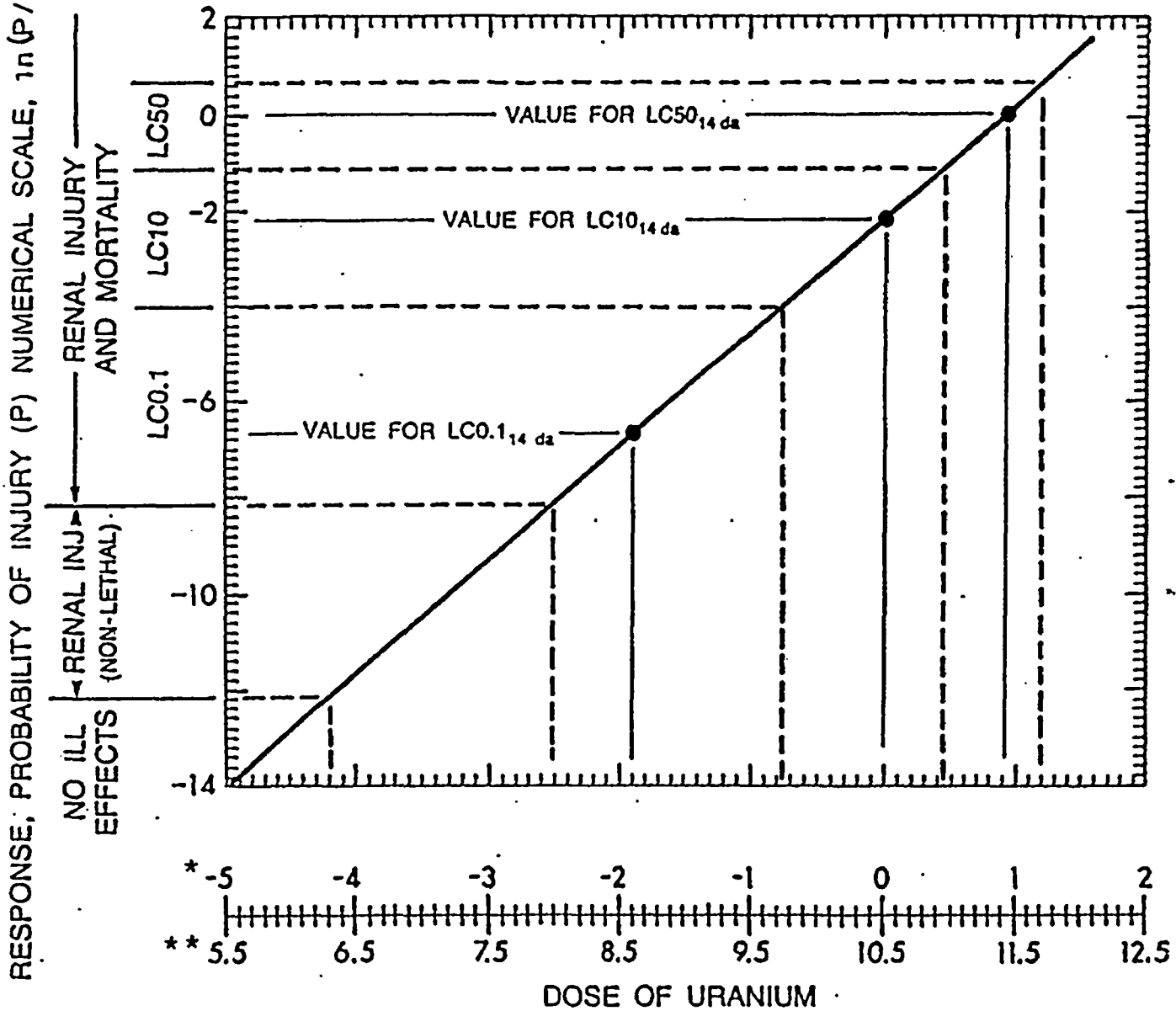
MINUTES	HF (mg/m³) 34 x 10^{-4} / U (mg /m³) 1 x 10^{-2}	34 x 10^{-3} / 1 x 10^{-1}	34 x 10^{-2} / 1 x 10^{0}	34 x 10^{-1} / 1 x 10^{1}	34 x 10^{0} / 1 x 10^{2}	34 x 10^{1} / 1 x 10^{3}	34 x 10^{2} / 1 x 10^{4}	34 x 10^{3} / 1 x 10^{5}	34 x 10^{4} / 1 x 10^{6}	34 x 10^{5} / 1 x 10^{7}	34 x 10^{6} / 1 x 10^{8}	34 x 10^{7} / 1 x 10^{9}	34 x 10^{8} / 1 x 10^{10}
0													
1	S	S	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L
2	S	S	S	S	S	I	L.1 + I	L	L	L	L	L	L
3	S	S	S	S	S	I	L10 + I	L	L	L	L	L	L
4	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
5	S	S	S	S	S	L.1 + I	L10 + I	L	L	L	L	L	L
6	S	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L	L
7	S•	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L	L
8	S	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L	L
9	S	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L	L
10	S	S	S	S	I	L.1 + I	L50 + I	L	L	L	L	L	L

L = LETHAL TO MORE THAN 50% OF THOSE EXPOSED
L50 = LETHAL TO 50% OF THOSE EXPOSED
L10 = LETHAL TO 10% OF THOSE EXPOSED
L.1 = LETHAL TO 0.1% OF THOSE EXPOSED
S = "NO ILL EFFECTS"
I = INJURY (PRIMARILY NON-LETHAL RENAL)

FIGURE 8. DOSE—RESPONSE ESTIMATES FOR MAN ACUTELY EXPOSED TO THE HYDROLYSIS PRODUCTS OF UF_6

(Primarily based on adjusted animal data from Leach *et al*, 1984)

$$UF_6 + 2H_2O \rightarrow UO_2F_2 + 4\ HF$$



* UPPER SCALE: ln OF ABSORBED DOSE OF URANIUM (mg U PER kg BODY WEIGHT)

** LOWER SCALE: ln OF CT PRODUCT (mg U/m^3 • min). C IS AIR CONCN. AND T IS EXPOSURE TIME

The data points on the graph are predicted values for $LC50_{14\ da}$, $LC10_{14\ da}$ and $LC0.1_{14\ da}$ through which a regression line has been drawn to define the areas of more subtle toxic changes such as non-lethal renal injury. The dotted lines roughly describe the 95% confidence intervals for the respective responses and have been adjusted to produce one interface between successive effects.

The principal advantage of this graphical display is that it clearly shows the relation between predicted health effects, the absorbed dose of U and the CT product of the exposure. These relationships are needed when evaluating the hazards of acute exposures to UF_6 and its hydrolysis products.

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Conclusions and Assumptions Basic to the UF_6 Exposure - Time Relationships

I. Background

(A) The new acute UF_6 exposure studies of Leach et al. (1983) provide important information in several key areas. Firstly, there is the extended observation that acute UF_6 toxicity is based primarily on the nephrotoxicity of the ^{+6}U ion except possibly under the most severe exposure conditions where some evidence of pulmonary injury also occurs. The associated upper airway injury could also be due to the action of HF gas. At the present time, one can only consider this evidence of pulmonary injury as an additional effect which does not modify the lethal outcome of acute UF_6 exposures except temporally. The acute toxicity of uranyl uranium is based on achieving a certain renal uranium level. This toxic level can result from a myriad combination of ^{+6}U concentrations and exposure times (minutes, hours, up to a few days) because renal uranium retention is rather persistent (half-time measured in weeks to months) in comparison to the durations of acute exposure.

(B) The new UF_6 studies (Leach et al., 1983) suggest that the absorbed fraction may be smaller with very high ^{+6}U concentration (> 100 g U m^{-3}) exposures probably due to less deep lung penetration and absorption; consequently, the CT product of a 2 minute exposure is at least a factor of 2 higher than any equally lethal CT combination acquired over longer times (5-60 minutes). In other words, very high airborne uranium concentrations (> 100 g m^{-3}) may be somewhat less efficient in delivering a lethal dose than lower airborne concentrations when the time is proportionally adjusted.

This statement should not be construed to mean that equal CT products should be expected to yield equal biological responses. This is not axiomatic in toxicolgy. When it does apply, the time interval is usually very limited and the dose-response data have the same slopes. The Leach et al. data indicate that the CT product for the acute lethal dose response in rats cannot be presumed constant between 2-10 minutes, although the dissimilarities at the LC50 level are not major ones.

(C) In the recent studies of UF_6 by Leach et al., one airborne U concentration, which was not effective in producing renal injury (biochemical changes) in rats, was approximately 0.44 g m^{-3} during a 2 minute exposure. However, with 5 mins of exposure, a concentration of 0.58 g U m^{-3} was clearly injurious to the kidneys. Assuming a 150 ml minute volume for the rat and a 0.3 absorbed fraction (Leach et al., 1983), then the following estimated absorbed doses result:

$$2 \text{ min} \times 0.15 \text{ l min}^{-1} \times 440 \ \mu\text{g U l}^{-1} \times 0.3 = 40 \ \mu\text{g U/rat}$$

$$5 \text{ min} \times 0.15 \text{ l min}^{-1} \times 580 \ \mu\text{g U l}^{-1} \times 0.3 = 130 \ \mu\text{g U/rat}$$

Assuming the rat weighed 250 g, then a factor of 4 converts the absorbed dose per rat to absorbed dose per kg, i.e. 0.16 mg U kg^{-1} and 0.52 mg U kg^{-1}, respectively. These estimated doses are completely consistent with those reported in the subacute toxicity studies (Morrow et al., NUREG/CR 2268, 1982), wherein absorbed or injected doses of 0.1 mg U kg^{-1} were found to be close to the renal injury threshold in the naive rat, whereas 1 mg kg^{-1} was definitely injurious by all criteria.

(D) In this same 1982 study, the rat, dog and human data were reported to be qualitatively similar, but evidence indicated the rat was less susceptible to

U-induced renal injury than the dog by nearly a factor of 10. Earlier human studies (Rochester and Boston) at the lowest administered ^{+6}U doses, seemed to yield results which were the most comparable to 1982 study with dogs and rats, with respect to U excretion and injury. On the basis of this level of dose-effect comparison, man appears to have an intermediate susceptibility.

The 1983 rat and guinea pig studies of Leach et al. show that the rat is also a more resistant specie than the guinea pig. On the basis of LC50's, a factor of 2 is indicated, but on the basis of extrapolating the dose-response curve to the LC0.1 region, the difference appears much greater, perhaps a factor > 20. This evidence on multispecie susceptibility is far from definite, but collectively it suggest that direct dose per body weight scaling of the rat data will underestimate the renal toxicity in man by possibly a factor of 2 to 7. These factors come from interpolating between the 0.16 mg kg^{-1} and the 0.5 mg kg^{-1} doses taken from the new UF_6 rat study, and the 0.07 mg kg^{-1} cited as the minimal dose found to produce renal injury in the human studies with intravenous uranyl nitrate (Morrow et al., 1982). It is also relevant to note that according to the recent report of Smith and Gelein (1982), uranyl fluoride appears to be somewhat more potent in its renal effects than uranyl nitrite, so it would be prudent to assume at least a factor of 7 between rat dose-effect and human dose-effect data expressed as absorbed U per kilogram body weight.

(E) On the basis of the propositions put forth in (D), it follows that an absorbed dose of around 0.01 mg U kg^{-1} (20 μg kg^{-1}) represents a dose which will produce minimal, probably "acceptable", injury in more susceptible human subjects and probably no detectable injury in the average person.

By the same reasoning, the rodent lethality data deserve at least this factorial adjustment, i.e. reduction by 7. Furthermore, one has to consider the fact that any dose-response analysis such as the LC50 leads to a probability distribution of responses; subjects will die at exposure levels below that producing the LC50, while others will survive that same dose. Consequently, if one takes the rat lethality dose-response data at 2 mins exposure, for example, the LC50 is 120 g U m^{-3}, the LC10 is around 55 g U m^{-3} and the LC0.1 appears to be around 10 g U m^{-3}. Thus, a variable degree of risk can be derived from these data. Unfortunately, a specific or acceptable degree of risk is not implicit in the usual dose-response matrix (e.g. Finamore and Crowley, 1980), be the criterion, death or injury. Moreover, the use of a particular risk analysis and the establishment of an acceptable risk level must be tied to its intended application. A level of risk deemed acceptable to a worker is not credible for a member of the public. Risk levels for injury and death must differ. Even death by different means necessitates different levels of "acceptability" due to the stigmata of certain means of dying e.g. by cancer. In ICRP, a 10^{-4} risk factor is applied to workers and 10^{-5} or 10^{-6} to the public indicating that a risk level should not exceed 0.01 percent lethality or 1 in 10,000. Thus even a LC0.1 estimation is inadequate for such risk levels; moreover, estimations of a ten-fold lower incidence of lethality is statistically impractical without a hundred-fold increase in the number of animals tested by Leach et al. (1983).

(F) The 1982 study of Morrow et al. and the subsequent study of Smith and Gelein (1982) both indicated that reversibility of renal injury induced by ^{+6}U was not a certainty. Clearly, there were major and persistent

distinctions between naive and previously-exposed subjects in their responsiveness to ^{6+}U administration. The bases for these distinctions appear to be related to a renal regeneration or repair process, but this process does not equate to a return to "normal" renal function. It may prove advantageous to the subject to have acquired a previously-exposed status especially if certain criteria are used, e.g., less susceptible to lethal injury. But this is a matter requiring much further evaluation before it could be rationally considered as a safety factor in a worker population. It has no relevance to exposure of the public in any case.

(G) If one takes the 2 min LC0.1 in the rat as a basis for intraspecies extrapolation, then 10 g U m^{-3} would be reduced to 1 g U m^{-3} on the basis of relative susceptability of rat versus man. See (D). Using this example, it is also prudent to keep in mind that beside a variation in response to a single dose level, there is an uncertainty in the dose estimated for a single response, consequently, a LC50 and a LC0.1 both require confident limits (see Leach et al., 1983) and these differ. Even when a specific lethality response is attributed to a single dose, this leaves an unknown factor to reduce to the lethality risk to an "acceptable" level. This could easily result in a limiting ^{+6}U concentration of several hundred milligrams per m^3 for any exposure equalling or exceeding 2 minutes. For exposure shorter than 2 minutes, the matter is far more conjectural. There are no experimental data to work with. The possibility of breath holding and other life saving manuevers are more realistically invoked with brief exposures. So it is conceivable that more than 1 g U m^{-3} as UF_6 could be tolerated for a fraction of a minute without lethal consequences.

II. Calculations of Lethal, Injurious and "No-Effect" Doses

The confidence limits on the $LC50_{14}$ data suggest ~20 g U m^{-3} x min as the minimal CT product capable of killing half of the rats. The LC0.1 data which are cited suggest that a CT product exceeding 10 g U m^{-3} x min would be expected to kill an occasional rat and more likely to kill a small percentage of exposed workers due to the relative susceptibilities. Taking into account the statistical uncertainties of the exposure data for this exposure-response region and the susceptibility differences, the 10 g U m^{-3} x min value is probably unconservative by a factor 10 to 25, suggesting a 1 g U m^{-3} x min exposure might constitute a minimally lethal level. In the $LD50_{14}$ case, a 2-minute exposure with a 7.5 ℓ minute volume (ICRP 30-Reference Man) leads to a 10 mg U ℓ^{-1} x 2 min x 7.5 ℓ min^{-1} = 150 mg U intake. The $LC0.1_{14}$ data by the same reasoning becomes 0.5 mg U ℓ^{-1} x 2 min x 7.5 ℓ min^{-7} = 8 mg U intake. Assuming 0.43 absorption (ICRP 30 for 1 μm MMAD aerosol), the predicted absorbed dose per kilogram body weight become ~ 1 mg U and ~ 0.05 mg U, respectively.

The absorbed dose producing an "acceptable" probability and degree of renal dysfunction is around 0.01 mg U kg^{-1} (see E), whereas a 0.1 mg U kg^{-1} dose is unacceptable in that this dose is expected to produce frank renal injury with evidence of non-reversibility (see C and D).

It should be remembered that in the foregoing analysis of absorbed doses, the lethal dose-response and injury dose-response data provide a continuum of

dose-response information. In the case of UF_6, the 0.05 to 1 mg U kg^{-1} dose-lethality data are associated with a stochiometric amount of HF. At the acutely toxic levels of U exposure, the HF level could have contributed to lethality (see A). In the overlapping 0.01 to 1 mg U kg^{-1} injurious-dose region, the effect of HF is believed to be unimportant (Morrow et al., 1982). Below 0.01 mg U kg, a region of "acceptable" (no effect) levels of absorbed dose is presumed to exist and the associated HF levels are definitely irrelevant.

The foregoing summarization indicates a "steep" dose-response relationship for UF_6 toxicity, i.e. the range of dose from minimally injurious to frankly lethal subtends a comparatively limited dose range. It is not unexpected therefore, that estimations of non-lethal injury and lethal injury limits overlap.

III. Exposure-Response Matrix

The estimates from part II, which included rounding-off of values, are basic to the following exposure-response matrix. Since the exposure is a concentration- and time-dependent phenomenon, the absorbed doses per kilogram body weight are first converted to total doses; then converted to intakes $\frac{(\text{total dose})}{0.43}$ and finally factored into various air concentration, exposure time components assuming a 7.5 $\ell\ \text{min}^{-1}$ ventilation which applies to sedentary work states (ICRP 30). If a more active work state is of interest, e.g. 20 $\ell\ \text{min}^{-1}$, the matrix concentration values would be reduced by 2.67 $(\frac{20}{7.5})$, or else the exposure time would be reduced by 2.67 if the matrix concentrations prevailed.

Three response regions are implied by the matrix. A "no-effect" region derived from human data and signified by a maximal concentration; an injurious-dose region, which extends from the maximal no-effect dose to an arbitrary minimally-lethal level; and a frankly lethal dose level, based on a slightly conservative LC50 relationship derived from the animal data.

Airborne Concentration mg M^{-3}

Time (mins)		Maximum "No effect" (0.01 mg kg^{-1})	Injury **	Lethality (LD50) (1 mg kg^{-1})
0.5	U^{+6} HF	4×10^2	2×10^3	4×10^4 1.4×10^4
2	U^{+6} HF	1×10^2	5×10^2	1×10^4 3.4×10^3
10	U^{+6}	20	1×10^2	2×10^3
30	U^{+6}	6	30	6×10^2
60	U^{+6}	2.5	10	3×10^2

** The response range termed "Injury" is given by a single value. This value can be considered to be the highest injury level which is not regarded as life threatening. However, this level is expected to produce relatively prolonged urinary biochemical abnormalities and histologically-evident renal damage.

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ESTIMATION OF HUMAN RESPONSE TO INHALED UF_6 HYDROLYSIS PRODUCTS

Report to Union Carbide Nuclear Division

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Objective:

The objective of this report is to review pertinent toxicologic and metabolic literature on uranium and from it estimate, as accurately as possible, the level at which short term exposure to the hydrolysis products of UF_6 will produce in man, no effect, irritation, temporary reparable physiological damage, permanent non-reparable physiological damage, and lethality for 50% of the exposed population. No safety factors have been incorporated in the analysis.

The estimate requested will be made by identifying concentrations of soluble U compounds in human studies (in mg/kg injected) known to cause or not cause (1) changes in urine and blood chemistry and (2) histopathological changes in the kidney. Work in animals is used to supplement the judgment process and to extend the estimation to include lethal concentrations.

Secondly, concentrations in air which would lead to the pharmacologic doses expressed as mg U/kg body weight necessary to induce effects will be estimated, using a simple metabolic model for inhaled UO_2F_2. Work in rats, dogs and man suggests strongly that such a simple model is appropriate (Mo80, Le83, Hu73).

Choice of Pharmacologic Doses for Estimated Biological Endpoints:

An important set of measurements in man consists of urine and blood chemistries in 6 patients injected intravenously with uranyl nitrate in sodium acetate, in dosages ranging from 0.006 to 0.071 mg/kg circa 1948. The subjects varied in age from 21 to 61; 2 were female. They had serious but not immediate life threatening conditions such as cirrhosis of the liver, ulcers, arthritis, and undernutritition. Urine was measured for catalase and urinary protein. No changes were seen for doses of 0.030 mg/kg or below and only marginal increases in catalase and protein for the doses at 0.042 and 0.070 mg/kg (Hu73).

Luessenhop et al. studied five mostly comatose patients with terminal brain tumors using injected doses of uranyl nitrate in sodium acetate ranging from 0.07 to 0.28 mg/kg. Striking changes in urinary catalase and protein from control levels (prior to injection) were seen in 3 subjects receiving 0.13, 0.17 and 0.28 mg/kg. Cellular debris, indicative of some pathology in the kidney, was observed in urine on days 2 through 9 in the two higher dose subjects, with a return to normal thereafter. An increase in urinary output followed all injections save one. Based on animal studies, increase in urinary glucose is supposed to be the most sensitive indicator of kidney damage, but no urinary glucose was found in any of the patients. This suggests, but does not prove, that the injury to the kidney was reparable and certainly not immediately life threatening. At autopsy, which was with one exception later than 42 days post injection, acute tubular damage was no longer visible (Lu58, Hu73).

Stevens et al. (1980) studied the pathology of injected ^{233}U (0.3 mg/kg) in seven dogs, and in one dog injected with ^{238}U. Blood urea nitrogen (BUN) was elevated in all animals throughout the duration of tests, up to 2 years for ^{233}U, but not for ^{238}U. Stevens et al. suggest the higher alpha dose for ^{233}U exacerbated the initial kidney lesions produced by the chemical toxicity of uranium. By 1 to 2 years post injection the ^{233}U content of the kidney was quite small, but hypertrophy of many of the collecting tubules and thick ascending limbs was prominent. Upon autopsy of one dog given 0.3 mg/kg ^{238}U intravenously, no histologic evidence of kidney pathology was seen using conventional light microscopic examination several years after administration, although a transient increase in blood urea nitrogen was noted in the weeks following exposure (see Figure 1) (G.N. Taylor 1983, personal communication). The work by Stevens et al. suggests that as the specific activity of U increases, toxicity to kidney also increases,

so that the results cited here are valid only for natural, depleted, or slightly enriched uranium.

The fact is that there is insufficient work in animals to identify with confidence a borderline between transient and permanent kidney injury. Based on data available, 0.3 mg/kg is judged the best estimate for the dog and is adopted for man without change.

Boback (Bo00), in workers heavily exposed to U_3O_8 and UF_2, found no evidence of urinary protein, sugar, or cellular debris, even though urinary excretion of uranium was as high as 2.85 mg U/l of urine.

For a 75% excretion in 24 h, and a daily urine output of 1.4 l, this implies an absorbed dose of 5.3 mg/70 kg or less in these workers, or $\leq$ 0.07 mg/kg. Thus the absence of urinary indicators of damage is consistent with the injected cases summarized by Hursh (Hu73). Generally, occupational exposure to uranium has not readily produced a toxic response in man, even though past practices may have been relatively primitive compared to modern plant industrial hygiene programs (Wr75).

The size of a lethal dose is not known from direct observation in man. Luessenhop et al. estimated it would be about 1 mg/kg, based on the fact that in the rabbit, catalasuria began at about 1/10 the lethal dose, and in man catalasuria began at about 0.1 mg/kg. If the range is the same in man, then 1.0 mg/kg is about the lethal dose for man. Durbin and Wrenn reviewed LD_{50}'s for several species. The LD_{50}'s for man, dog, and rat are all about 1 mg/kg; mouse is less sensitive, while rabbit is much more sensitive (see Table 1) (Du75).

Based on this, the following categories for man are adopted for this analysis:

no effect	0.04 mg/kg	no change in urinary catalase or protein observed in man
irritation	78 mg U/m^3 in air	based on response to HF produced in UF_6 hydrolysis
onset of health effect	0.07 mg/kg	transient evidence of kidney damage, may be completely repaired without loss of significant kidney function
permanent health effect	0.3 mg/kg	possible loss of some kidney function, with definite histopathological changes in the kidney for several months, or possibly longer
lethal	1.0 mg/kg	value is approximate LD50 and likely not lethal to 100%

Estimating Effects for Inhalation Exposure to UF_6 Hydrolysis Products

The animal work in dogs and rats shows that absorption to the blood is rapid and complete, except for UO_2F_2 which is swallowed. The GI absorption of uranium which is swallowed is < 1%.

Thus the systemic dose will consist of that which is inhaled, deposited and translocated to blood. I adopt the ICRP lung model to estimate this fraction, which will depend on the particle size distribution. For 1 micron AMAD, the lung model (Class W) predicts 43% of that inhaled will translocate to blood. Morrow found 33% of the inhaled dose became systemic in the nose breathing rat (Mo82).

In Reference Man defined by the ICRP, the resting breathing rate is 7.5 l/min and the light activity breathing rate is 20 l/min. I will use both values to infer concentration values at which effects would be likely (IC75).

The air concentration and duration of exposure at which a dose of D_e (mg/kg) would be delivered is given by

$$C = \frac{mD_e}{Itf}$$

where I = the breathing rate in m^3/min,

t = time in minutes,

m = body mass of Reference Man, 70 kg,

f = fraction of inhaled uranium which becomes systemic, 0.43.

This reduces to

$$C = \frac{163\ D_e}{It}$$

which is solved for the various D_es and both resting and light activity breathing rates; the results are shown in Table 2.

The predictions appear consistent for 60 minute exposure times with observations in the rat, where an $LC_{19d}^{57\%} < 0.71$ gm/m^3 (4 of 7 rats died in 19 days) was found by Morrow et al. (Mo82).

The results reported by Leach et al. for 2, 5, and 10 and 60 minute exposure are summarized as follows (Le83,Lea83):

t (minutes)	LC_{15}^{50} (g U/m^3)	t x LC_{15}^{50} (g-min/m^3)
2	120	241
5	39	193
10	12	120
60	0.74	44

The data on 2, 5, 10 and 60 minute exposures show clearly (column 3) that increasing exposures in gram-minutes/m^3 are required to produce the same effect. Thus toxicity was not linearly related to the product of time and concentration in the rat with short time exposures. This may reflect altered breathing rates and/or particle agglomeration and reduced pulmonary deposition at these high concentrations, or other effects. The data at 60 minutes relative to 10 minutes suggests there is a drop by a factor of three or greater in the g-minutes/m^3 LC_{15}^{50} exposure required to produce equivalent degrees of lethality. From 60 to 2 minute exposures, the ratios of g-min/m^3 to produce equivalent LC_{15}^{50} increases by a factor of 5.5.

Thus the more prolonged the exposure in the range of 2 to 60 minutes, the greater the apparent toxicity, and the lower the concentration needed to produce lethality. This suggests that the values for <u>lethality</u> only in Tables 2 and 3 may be increased by as much as a factor of 5. In the absence of an understanding of the mechanism, I have not made any such adjustment as predictive for man.

For a 60 minute exposure, the values for a LC_{30}^{50} for man, 0.14 to 0.36, are below the LC_{15}^{50} for rat, 0.7. Thus the rat appears to be an approximate, but probably appropriate, surrogate for man for lethal concentrations.

<u>Concomitant toxicity of HF:</u>

Although I am not as familiar with the literature on toxicity of HF and fluorides, I have reviewed part of it and made estimates based on the following assumptions.

First UF_6 hydrolyzes completely and the stoichiometric mass ratio of U:HF, which is 1:0.34, represents the relative amount of HF available to breathe.

The analysis which follows is based primarily on literature in animals and man dealing with HF toxicity (Ms82).

From Table 3, it is clear that inhalation of HF by rats for time periods between 5 minutes and 6 hours leads to a high proportion of lethality for t x C in the range of 53 to 72 mg F-min/m^3. Thus the product of concentration and time which is an LC50 will be taken as 50 mg F-min/m^3. Exposures to rats at 1300 mg F/m^3 for 15 to 30 minutes produced necrosis and inflamation of the nasal epithelium, but no low respiratory tract pathology. This is equivalent to t x C = 20 to 39 mg F-min/m^3.

There are several reported lethal accidents with HF. In one splash burn with HF, death occurred from heart failure subsequent to a fluoride induced hypocalcemia, refractory to clinical management (Te80). Fluoride precipitates Ca in blood, which is the apparent mechanism producing the hypocalcemic state. Prompt treatment may eliminate a fatal reaction. Ingestion of milk may help to convert soluble fluoride compounds in the stomach and small intestine to the less soluble calcium salts.

The lack of pulmonary pathology in animals suggests exposure for HF has been to large particles removed in the upper airway. Whether absorbed from the nasal epithelium or in the G.I. tract, absorption of HF deposited anywhere in the respiratory tract will be either very high or complete. Gastric symptoms from excess HF acidity in stomach have been reported and the vomitus of a severely exposed individual is capable of inducing external burns.

I have not been able to identify a level producing permanent but sub-lethal pathological consequences.

To analyze the expectations I chose the following levels.

HF Effects in Man

no effect	2.5 mg F/m^3	indefinite time (t)	may be tasted
irritation	25 mg F/m^3		not tolerable for more than 1 min at 100 mg/m^3
lethal	50,000 mg F-min/m^3		lethal in high proportion of rats exposed to HF for 150 mg/m^3 to 14,000 mg/m^3 for 5 min to 6 h

Thus $C = \frac{(Ct)e}{t}$ for lethality using $(Ct)_e = 50{,}000$ mg F-min/m^3.

t	C (mg/m^3)	mg F/m^3 associated with the LD_{30}^{50} for U for resting breathing rate (from Table 2)
0.5	100,000	13,900
2	25,000	3,500
5	10,000	690
10	5,000	230
60	833	120

Thus, since the expected HF concentrations in air from hydrolysis of UF_6, at levels where effects of U on kidney may be lethal, are smaller than the LC50 concentrations for HF, uranium toxicity is controlling. However, HF will probably kill faster, and the experiments by Leach et al in the rat at high UF_6 loadings may well reflect HF toxicity rather than U toxicity.

Noticeable irritation of the nasal mucosa will occur at HF exposures of 25 mg/m^3 or greater, and 100 mg/m^3 has been called intolerable for more than 1 minute. This is equivalent to a U concentration of 78 mg/m^3, which is less than any concentration of U likely to induce permanent kidney damage for resting breathing rates (see Table 2). Thus irritation and an avoidance response in man is probably controlled by the HF hydrolysis product of UF_6 at concentrations below those likely to produce kidney injury from the exposure to uranium. Thus people involved in accidental exposures to airborne UF_6 able to take action to avoid breathing it further would do so at lower concentrations than those likely to produce kidney injury.

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TABLE 1
(from Du75)

TABLE 2. Toxicity of $UO_2(NO_3)_2 \cdot 6H_2O$ administered to animals, expressed as $LD_{50}/30$.

	Exposure	Single injection[a,b] (mg U/kg)	30 daily i.p. injections[b] (mg U/kg/day)	30 daily feedings[c] (mg U/kg/day)	30 inhalation exposures[c] (mg U/kg/day)
Animal	Rabbit	0.1	—	23	0.07
	Guinea pig	0.3	—	—	1.7
	Dog	2.0	—	47	0.42
	Cat	—	—	—	0.1 – 0.2
	Rat[e]				
	male	2	0.38	1070	1.6
	female	1	—	—	—
	Mouse				
	albino	6 – 8	—	—	1.7
	C_3H	20 – 25	—	2000	—

[a] Haven and Hodge,[56] Tannenbaum and Silverstone.[57]

[b] Maynard et al.[32]

[c] Dog, Haven and Hodge;[56] rabbit, calculated from data of Haven and Hodge[56] assuming 150 g/day eaten by 3-kg rabbit; rat, calculated from data of Maynard et al.[32] assuming 11.2 g/day eaten by 0.2-kg rat; mouse, calculated from data of Tannenbaum and Silverstone.[57]

[d] Calculated from data of Dygert et al.[32] on combined lethality of UF_6, UO_2F_2, and $UO_2(NO_3)_2 \cdot 6H_2O$ assuming minute volumes and average body weights as follows: dog, 3000 ml/min, 10 kg; rabbit, 700 ml/min, 3 kg; guinea pig, 115 ml/min, 0.3 kg; rat, 118 ml/min, 0.2 kg; mouse, 27 ml/min, 0.03 kg. The equation is shown in legend of Fig. 20.

[e] All other rat data are for males and females combined.

TABLE 2

Concentrations of U in Air at Times of Exposure Associated with Various Responses in Man in mg U/m^3 Air

t (min)	No observable effect 0.04 mg/kg	Onset of damage 0.07 mg/kg	Permanent damage 0.3 mg/kg	LC 50/30 LD 50/30 is 1.0 mg/kg
Resting (7.5 l/min breathing rate)				
0.5	1,740	3,040	13,040	43,500
2	435*	760	3,260	10,900
10	87	150	650	2,170
30	29	51	217	724
60	14	25	109	362
Light Activity (20 l/minute breathing rate)				
0.5	652	1,140	4,890	16,300
2	163	285	1,220	4,070
10	33	57	245	815
30	11	19	81	270
60	5.2	9.4	41	136

* Leach et al conclude that there are no measurable effects on rat kidney, based on pathological examination of tissue from animals sacrificed at 14 days exposed to UF_6 for 2 minutes at a concentration of 440 mg U/m^3.

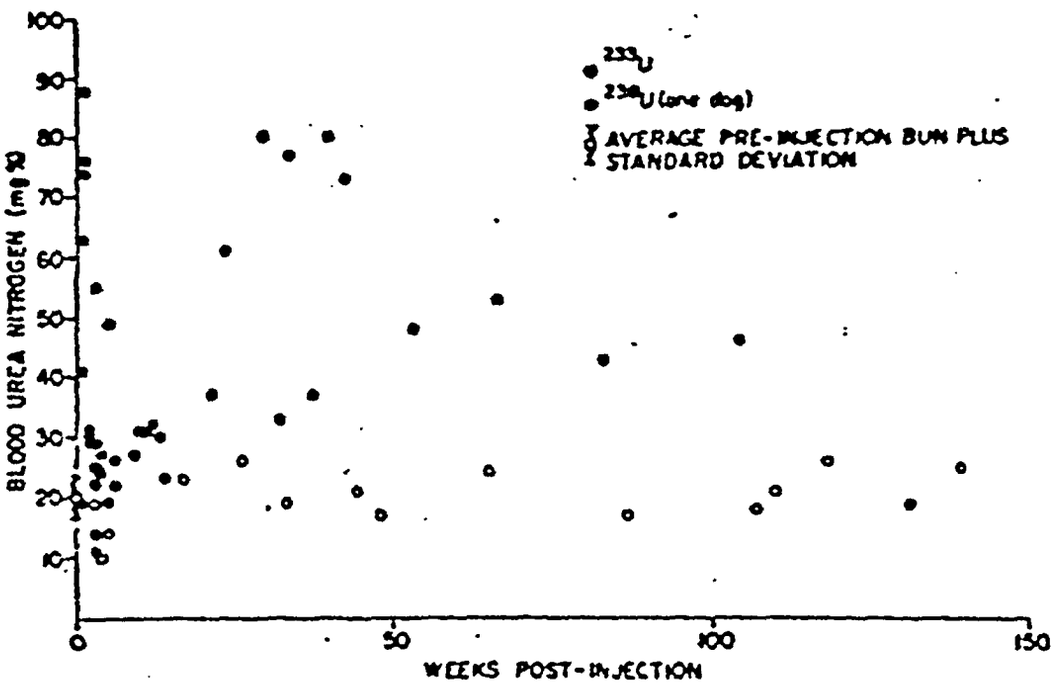
In practice, these concentration estimates should generally be rounded to one significant figure, or at most two.

TABLE 3

Results of exposure to HF

Animal	t	C (mg F/m^3)	10^{-3} Ct(min)	Remarks	Ref.
rat	15-30 min	1300	20-39	necrosis and inflama- inflamation of nasal epithelium. No lower respiratory tract pathology	(Ro63)
rat	6 h	148	53	LC100 in 3 hours. No signs of pulmonary damage	(No79)
rat	5 min	14,400	72	LC100 in 5 minutes	(Di71)
rat	60 min	1100	66	LC50 in 60 minutes	(Wo76)
dog	309 h over 50 days	5.7	263	damage to lung and liver	(Wa78)
dog	5 weeks	< 3.3		emphysema in dogs	(Wa78)
guinea pig	50 days	6.7		$LD_{50d}^{2/3}$	(Wa78)
man		25		irritation of lower airway	(Me34)
man		2.5		NIOSH occupational standard	(NI76)

FIG. 1



BLOOD UREA NITROGEN VALUES IN BEAGLES AT VARIOUS INTERVALS FOLLOWING A SINGLE INTRAVENOUS INJECTION OF ~2.8 μCi ^{233}U/kg OR ~000 μCi ^{238}U/kg

(Taylor, 1983)