

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#: NOT PROVIDED

N-13-LABELED AMMONIA

REVIEWER:

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SUBMISSION TYPE: LITERATURE REVIEW

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I. SYNOPSIS/BACKGROUND

This is a pharmacokinetic review of N-13 labeled ammonia (N-13 ammonia). N-13 ammonia is currently used with positron emission tomography (PET) mainly to measure myocardial blood flow in a noninvasive manner. The information provided in this review is obtained from the literature articles provided by the Agency. The literature articles are considered to constitute an NDA. This review is, therefore, in the format of a normal NDA review. In addition, the list of literature articles cited is included in this review.

N-13 ammonia emits a positron particle which ultimately annihilates with an electron and yields two gamma rays, each with an energy of 511 keV. The physical half-life of N-13 ammonia is 9.96 minutes.

In the literature information reviewed, N-13 ammonia is administered intravenously for PET procedures. The dose range is 8-25 mCi. In one literature article, the specific activity range is stated as 200-400 mCi per micromole. This amounts to an N-13 ammonia dose of 0.020-0.040 micromole for the 8 mCi dose and 0.0625-0.125 micromole for the 25 mCi dose. Therefore, it is reasonable to expect that the amounts of N-13 ammonia injected for PET imaging would not cause significant changes in the amounts of endogenous ammonia produced daily in the body by various biochemical mechanisms.

Following intravenous administration to humans, N-13 ammonia is metabolized to N-13 labeled urea (N-13 urea, the most abundant metabolite), N-13 labeled neutral amino acids, mainly N-13 labeled glutamine (N-13 glutamine, the most important metabolite related to PET imaging) and traces of N-13 labeled amino acid anions (acidic amino acids) mainly N-13 glutamate and N-13 aspartate). N-13 urea is eliminated in urine and N-13 glutamine is "trapped" in the myocardial cells. Based on the data provided in the literature, it was estimated, in the review process, that in human blood, the biologic half-life and effective half-life of N-13 ammonia are 2.84 min and 2.21 min, respectively, and in human myocardium, its biologic half-life is less than 2 min and its effective half-life is less than 1.67 min. N-13 ammonia enters the brain by passive diffusion through the blood-brain barrier and is rapidly metabolized to N-13 glutamine with a half-life of 3 seconds or less. Due to the ultra short half-life of this PET imaging agent, it is considered that the standard pharmacokinetic parameters such as area under the blood/plasma concentration versus time curve, systemic clearance and apparent volume of distribution might be of limited value in the assessment of the safety and efficacy of the drug. Subsequently, no attempt was made to estimate such pharmacokinetic parameters from the limited blood data available in the reviewed literature articles.

The dosimetry data (in mGy/MBq) for N-13 ammonia has been determined by the "Task Group of Committee 2 of the International Commission on Radiation Protection" (ICRP) for adults and pediatric groups 1, 5, 10 and 15 years old. For each age group, the organ with the highest absorbed radiation dose per unit activity is the kidney. In general, the absorbed radiation doses per unit (administered) activity for pediatrics who are 15 years old appear to be similar to adult values but the values for pediatrics 10 years old or younger appear to be significantly higher. In

this review process, the ICRP dosimetry data have been converted to units of rem/mCi that are commonly found in regulatory documents. The derived dosimetry values have been applied to the upper dose range of N-13 ammonia (25 mCi) stated in the reviewed literature articles in order to help enhance the medical officer's position in making safety decisions that relate to the dosimetry of the drug.

It is noted that the adult dosimetry values for the kidney determined by two other groups of investigators Gewirtz, et al. and Meyer, et al. are, respectively, 70% and 127% higher than that determined from the ICRP data in the review process (see page 8 [item 12]). These data suggest that differences in dosimetry data determined by different workers in different laboratories could be significant.

A three compartment model is used to describe the kinetics of N-13 ammonia as it relates to its use in the measurement of myocardial blood flow by the PET technique. The blood compartment represents N-13 ammonia in the coronary capillaries. The extravascular compartment represents N-13 ammonia in the extracellular space of the myocardium. The metabolic compartment represents the N-13 ammonia that has entered the intracellular space of the myocardium, has been converted to N-13 glutamine by glutamine synthase and has remained trapped within the myocardial intracellular space. In this model, the rate constant, K1 represents the delivery of blood to the myocardium (mass specific blood flow [F]) as well as the fraction of the tracer that permeates the coronary capillary and enters the myocardial tissue (single pass extraction fraction [E]). Thus, K1 represents the product of F and E, that is, $K1 = FE$. **K1 is determined from the differential equation that describes the three compartmental model.**

N-13 ammonia is highly extracted from blood. Its E values are assumed to be greater than 0.9 (i.e., approaches 1.0) even at flow rates as high as 500 mL/min/g of myocardial tissue. Thus, for practical purposes, F values are approximately equal to FE values and F is approximately equal to K1. **Therefore, the K1 value obtained for the three compartmental model for N-13 ammonia is the value of myocardial blood flow.** This model yields myocardial blood flow values that are comparable to those obtained by other techniques such as coronary angiography and Doppler catheterization. Therefore, this model appears to be adequate for estimating myocardial blood flow in N-13 ammonia PET procedures.

The purpose of this review is **not** to determine the suitability of the three compartmental model for the measurement of myocardial blood flow. This review is undertaken in order to obtain insight into the type of pharmacokinetic information presented in the literature for N-13 ammonia when used with PET. The ultimate goal is to be able to make a rational decision as to the nature of the pharmacokinetic information that should be required by the Agency from sponsors that wish to submit NDAs for PET procedures that utilize N-13 ammonia.

Based on the information contained in the reviewed literature articles, it is considered that for PET (and other procedures) utilizing intravenous doses of N-13 ammonia, pharmacokinetic information need not be required.

II. SUMMARY OF INFORMATION ON PHARMACOKINETICS, PHARMACODYNAMICS, METABOLISM, PLASMA PROTEIN BINDING, DRUG INTERACTIONS, ETC.

1. **RADIOACTIVITY DOSE:** The dose range of N-13 ammonia indicated in the reviewed literature articles is 8-25 mCi¹⁻¹⁷.

2. **TOTAL AMMONIA DOSE RANGE:** In one literature article¹, an N-13 ammonia specific activity range of 200-400 mCi per micromole is reported. Considering the above dose range, this amounts to a total N-13 ammonia dose of 0.02-0.04 micromole for the 8 mCi dose and 0.0625-0.125 micromole for the 25 mCi dose. Therefore, it is reasonable to expect that the amounts of N-13 ammonia injected for PET imaging would not cause significant changes in the amounts of endogenous ammonia produced daily in the body by various biochemical mechanisms.

3. **METHOD OF BLOOD SAMPLE ANALYSIS:** Analysis of N-13 ammonia and its metabolites in blood samples was performed mostly by the batch elution method on a series of ion exchange resins^{1,2}. The most accurate method for this purpose, the radio-HPLC method¹ was not used in the studies reported in the reviewed literature articles because the levels of analytes from the low doses of N-13 ammonia administered (20 mCi or less in most cases) were too low to be reliably quantified by this method.

4. **BLOOD KINETICS:** The N-13 label of N-13 ammonia undergoes physical decay to carbon-13 (C-13) with a half-life of 9.96 minutes. In one of the reviewed articles¹, the percentages of the injected dose of N-13 labeled ammonia in human blood at 1, 2, 3, 4 and 5 min were 93.1%, 94.0%, 81.8%, 74.7% and 50.2%, respectively (Table 1). The blood elimination half-life estimated from these data, in the review process, is approximately 2.84 min. Based on these data, the effective blood half-life of N-13 ammonia is approximately 2.21 min (physical decay half-life = 9.96 min). Due to the ultra short half-life of this PET imaging agent, it was considered that the standard pharmacokinetic parameters such as area under the blood/plasma concentration versus time curve, systemic clearance and apparent volume of distribution might be of limited value in the assessment of the safety and efficacy of the drug. Subsequently, no attempt was made to estimate such pharmacokinetic parameters from the limited blood data available in the reviewed literature articles.

TABLE 1.
Distribution of Radioactivity in Human Whole Blood after [¹³N]ammonia Administration*

Metabolite	% Metabolite [†]				
	1 min (n = 6)	2 min (n = 7)	3 min (n = 8)	4 min (n = 8)	5 min (n = 5)
Ammonia	93.1 ± 4.9 (85.7-98.9)	94.0 ± 2.8 (90.0-95.9)	81.8 ± 10.5 (63.1-99.1)	74.7 ± 13.4 (56.9-97.5)	50.2 ± 18.9 (26.0-75.0)
Urea	3.1 ± 4.6 (0-10.0)	1.5 ± 1.9 (0-6.2)	7.2 ± 7.3 (0-23.2)	11.1 ± 9.2 (0-28.3)	32.7 ± 10.0 (23.8-49.1)
Neutral amino acids	3.0 ± 2.4 (0-6.5)	4.0 ± 1.5 (1.7-6.1)	10.4 ± 4.5 (0.9-15.5)	13.8 ± 7.5 (1.0-21.6)	16.2 ± 11.2 (0.2-27.9)
Acidic amino acids	0.8 ± 0.7 (0-1.7)	0.4 ± 0.5 (0-1.5)	1.1 ± 1.4 (0-1.5)	0.4 ± 0.3 (0.1-0.8)	0.9 ± 0.7 (0-1.7)

* Mean ± s.d. with range below in parentheses.

† Based on % of total-blood radioactivity.

5. **MYOCARDIAL KINETICS:** The myocardial kinetics of N-13 ammonia has been evaluated in normal volunteers under normal blood flow conditions (rest) and under conditions of accelerated blood flow (stress)³. The stress condition was induced using an intravenous dose of the vasodilator, dipyridamole. A region of interest was placed over the wall of the left ventricle and the left ventricle chamber. The uptake and retention of the N-13 activity was significantly greater under stress conditions (Fig. 1).

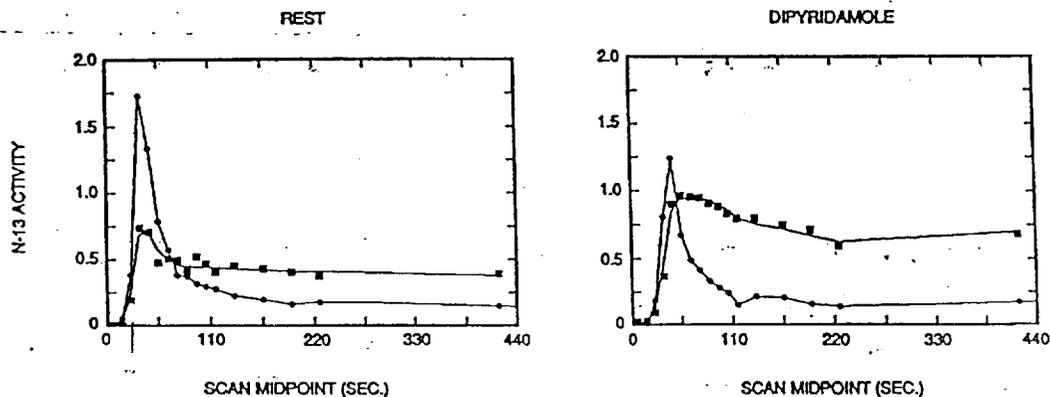


Fig. 1. Time-activity curves obtained from a region of interest placed over the left ventricular chamber (circles) and myocardial regions (squares). The plots on the left represent baseline (rest) condition. The plots on the right represent stress condition induced by an intravenous dose of dipyridamole.

Based on these data, it is estimated that myocardial N-13 activity reaches a plateau in approximately 1.5 min under normal flow conditions and 3.7 min under stress conditions. These data indicate significant trapping of N-13 activity in the myocardium suggesting that beginning at 1.5 min postdose under rest conditions and 3.7 min postdose under stress conditions, the N-13 activity present in the myocardium is mainly in the form of N-13 glutamine. Thus, N-13 ammonia is rapidly metabolized to N-13 glutamine in the myocardium under both rest and stress conditions. In the review process, it was estimated that in the myocardium, the biologic half-life of N-13 ammonia is less than 2 min and its effective half-life is less than 1.67 min.

6. **BRAIN KINETICS:** Intravenously administered N-13 ammonia enters the brain by passive diffusion, through the blood-brain barrier, and is rapidly metabolized to N-13 glutamine by glutamine synthase⁴. Its brain half-life does not exceed 3 seconds⁴.

7. **METABOLISM:** N-13 ammonia undergoes a five-enzyme step metabolism in the liver to yield N-13 urea (the main circulating metabolite)^{1,2}. It is also metabolized to N-13 glutamine (the main metabolite in tissues) by glutamine synthase in the skeletal muscle, liver, brain, myocardium and other organs^{1,2,4,5}. Other metabolites of N-13 ammonia include small amounts of N-13 amino acid anions (acidic amino acids) in the forms of N-13 glutamate or N-13 aspartate¹.

8. **URINARY EXCRETION:** N-13 urea, the main circulating metabolite of N-13 ammonia¹ is eliminated mainly in urine.

9. **PLASMA PROTEIN BINDING:** In the literature information reviewed, no information is provided on plasma protein binding of N-13 ammonia or its N-13 metabolites.

10. **MYOCARDIAL BLOOD FLOW ASSESSMENT WITH N-13 LABELED AMMONIA:** The kinetics of intravenously administered N-13 ammonia, as it relates to PET imaging, is best described by a three compartment model^{3, 5}. A schematic of this model is presented in Fig. 2.

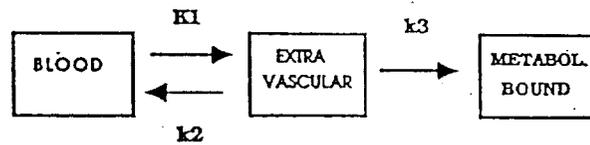


Fig. 2. Three compartmental tracer kinetic model describing extraction and retention of N-13 ammonia in myocardial tissue. K1 and k2 reflect exchange of N-13 ammonia between vascular and extravascular space in the myocardium and k3 represents metabolically trapped ammonia in the form of glutamine. (From Reference #3)

The blood compartment represents N-13 ammonia in the coronary capillaries. The extravascular compartment represents N-13 ammonia in the extracellular space of the myocardium. The metabolic compartment represents the N-13 ammonia that has entered the intracellular space of the myocardium, has been converted to N-13 glutamine by glutamine synthase and has remained trapped within the myocardial intracellular space.

The rate constant, K1 represents the delivery of blood to the myocardium (mass specific blood flow [F]) as well as the fraction of the tracer that permeates the coronary capillary and enters the myocardial tissue (single pass extraction fraction [E]). Thus, K1 represents the product of F and E, that is, $K1 = FE$. **K1 is determined from the following differential equation that describes the three compartmental model:**

$$\frac{dC_E(t)}{dt} = K_1 C_a(t) - k_2 C_E(t) - k_3 C_E(t) - \lambda C_E(t)$$

In this equation, $C_E(t)$ is the N-13 ammonia concentration in tissue (in mCi/g tissue), K_1 is the rate of N-13 ammonia uptake (in ml/g per min), $C_a(t)$ is the arterial blood content of N-13 ammonia (in mCi/mL of blood), k_2 is the N-13 ammonia washout rate constant (in reciprocal min), k_3 is N-13 glutamine formation rate constant (in reciprocal min) and λ is N-13 ammonia decay rate constant (in reciprocal min).

The N-13 glutamine trapped in the myocardium is determined from the following differential equation:

$$\frac{dC_G(t)}{dt} = k_3 C_E(t) - \lambda C_G(t).$$

In this equation, $C_G(t)$ is the N-13 glutamine concentration in tissue (in mCi/g tissue) and the other terms are as defined above.

N-13 ammonia is highly extracted from blood^{3,5}. Its E values are assumed to be greater than 0.9 (i.e, approaches unity [1.0]) even at flow rates as high as 500 mL/min/g of myocardial tissue. Thus, for practical purposes, F values are approximately equal to FE values. Therefore, F is approximately equal to K1. **Thus, the K1 value obtained for the three compartmental model for N-13 ammonia is the value of myocardial blood flow.** This model yields myocardial blood flow values

that are comparable to those obtained by other techniques such as coronary angiography and Doppler catheterization.

11. IMAGING TIME FOR MYOCARDIAL PERFUSION MEASUREMENT: PET imaging for measurement of myocardial perfusion begins at the time of N-13 ammonia injection and continues for about 10 minutes^{2,3}.

12. PHARMACOKINETICS IN SPECIAL POPULATIONS:

A. **RENALLY IMPAIRED PATIENTS:** In the literature information reviewed, specific information on the effect of renal impairment on the kinetics of N-13 ammonia has not been provided.

B. **HEPATICALLY IMPAIRED PATIENTS:** In the literature information reviewed, specific information on the effect of hepatic impairment on the kinetics of N-13 ammonia has not been provided.

B. **PEDIATRIC PATIENTS:** In the literature information reviewed, no information has been provided on the kinetics of N-13 ammonia in the pediatric population.

13. DOSIMETRY: The dosimetry data (in mGy/MBq) for N-13 ammonia determined by the "Task Group of Committee 2 of the International Commission on Radiation Protection" (ICRP)¹⁸ for adults and pediatric groups 1, 5, 10 and 15 years old are presented in Table 2. In the review process, this reviewer converted these data to radiation absorbed doses in rem/mCi that are more commonly found in regulatory documents (see in Table 3). The **adult adrenal** data are hereby used to illustrate the conversion process.

$$1 \text{ MBq} = 0.0023 \text{ mGy. Therefore, } 1 \text{ mCi (37 MBq)} = 0.0851 \text{ mGy.}$$

$$1 \text{ mGy} = 0.1 \text{ rad. Therefore, } 0.0851 \text{ mGy} = 0.00851 \text{ rad.}$$

$$\text{For N-13 ammonia, } 1 \text{ rad} = 1 \text{ rem. Therefore, } 0.00851 \text{ rad} = 0.00851 \text{ rem}$$

Thus, $0.0023 \text{ mGy/MBq} = 0.00851 \text{ rem/mCi}$.

Table 2. ^{13}N : ICRP Data for Radiation Absorbed Dose Per Unit Activity (mGy/MBq) for Adults and Pediatric Groups 1, 5, 10 and 15 Years Old

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 year	10 year	5 year	1 year
Adrenals	2.3E-03	2.6E-03	4.2E-03	6.7E-03	1.3E-02
Bladder wall	8.1E-03	9.9E-03	1.5E-02	2.4E-02	4.5E-02
Bone surfaces	1.6E-03	1.9E-03	3.1E-03	5.1E-03	9.9E-03
Brain	4.2E-03	4.4E-03	4.7E-03	5.2E-03	7.3E-03
Breast	1.8E-03	1.8E-03	2.8E-03	4.6E-03	8.9E-03
GI-tract					
Stomach wall	1.7E-03	2.1E-03	3.2E-03	5.2E-03	9.9E-03
Small intest	1.8E-03	2.2E-03	3.5E-03	5.6E-03	1.1E-02
ULI wall	1.8E-03	2.1E-03	3.4E-03	5.6E-03	1.0E-02
LLI wall	1.9E-03	2.1E-03	3.4E-03	5.4E-03	1.0E-02
Heart	2.1E-03	2.6E-03	4.0E-03	6.1E-03	1.1E-02
Kidneys	4.6E-03	5.7E-03	8.5E-03	1.3E-02	2.4E-02
Liver	4.0E-03	4.9E-03	7.8E-03	1.2E-02	2.3E-02
Lungs	2.5E-03	3.0E-03	4.8E-03	7.9E-03	1.5E-02
Ovaries	1.7E-03	2.3E-03	3.6E-03	5.7E-03	1.1E-02
Pancreas	1.9E-03	2.3E-03	3.7E-03	5.8E-03	1.1E-02
Red marrow	1.7E-03	2.1E-03	3.3E-03	5.5E-03	1.0E-02
Spleen	2.5E-03	3.0E-03	5.0E-03	8.0E-03	1.5E-02
Testes	1.8E-03	1.9E-03	3.1E-03	4.9E-03	9.5E-03
Thyroid	1.7E-03	2.2E-03	3.6E-03	5.8E-03	1.1E-02
Uterus	1.9E-03	2.4E-03	3.9E-03	6.1E-03	1.1E-02
Other tissue	1.6E-03	1.9E-03	3.0E-03	4.9E-03	9.4E-03
Effective dose equivalent (mSv/MBq)	2.7E-03	3.2E-03	4.9E-03	7.7E-03	1.5E-02

Table 3. ^{13}N : Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups 1, 5, 10 and 15 Years Old

Organ	Adult	15 year old	10 year old	5 year old	1 year old
Adrenals	0.0085	0.0096	0.016	0.025	0.048
Bladder wall	0.030	0.037	0.056	0.089	0.17
Bone surfaces	0.0059	0.0070	0.011	0.019	0.037
Brain	0.016	0.016	0.017	0.019	0.027
Breast	0.0067	0.0067	0.010	0.017	0.033
Stomach wall	0.0063	0.0078	0.012	0.019	0.037
Small Intestine	0.0067	0.0081	0.013	0.021	0.041
*ULI	0.0067	0.0078	0.013	0.021	0.037
**LLI	0.0070	0.0078	0.013	0.020	0.037
Heart	0.0078	0.0096	0.015	0.023	0.041
Kidneys	0.017	0.021	0.031	0.048	0.089
Liver	0.015	0.018	0.029	0.044	0.085
Lungs	0.0093	0.011	0.018	0.029	0.056
Ovaries	0.0063	0.0085	0.013	0.021	0.041
Pancreas	0.0070	0.0085	0.014	0.021	0.041
Red marrow	0.0063	0.0078	0.012	0.020	0.037
Spleen	0.0093	0.011	0.019	0.030	0.056
Testes	0.0067	0.0070	0.011	0.018	0.035
Thyroid	0.0063	0.0081	0.013	0.021	0.041
Uterus	0.0070	0.0089	0.014	0.023	0.041
Other tissues	0.0059	0.0070	0.011	0.018	0.035

*Upper large intestine, **Lower large intestine

These data suggest that for intravenously administered N-13 ammonia, for each of the organs evaluated, (i) the absorbed radiation doses per unit activity are similar for adults and pediatrics 15 years old or older (5 years old or older for the brain), (ii) for pediatrics 10 years old or younger (1 year old for the brain), the absorbed radiation doses per unit activity appear to be significantly higher than adult values (e.g., for the urinary bladder wall, the ratios of pediatric values to adult values for pediatrics 10, 5 and 1 year(s) old are, respectively, 2, 3 and 6, approximately), and (iii) for each of the age groups evaluated (i.e., pediatrics 1, 5, 10 and 15 year(s) old as well as adults), the organ with the highest radiation exposure is the urinary bladder wall.

The data presented in Table 3 could be used to estimate the organ radiation absorbed doses for a given intravenous dose of N-13 ammonia.

In the literature articles reviewed, the highest dose of N-13 ammonia administered is 25 mCi. Based on the data presented in Table 3, the absorbed radiation doses for this dose of radioactivity (25 mCi) have also been calculated, in this review process, for adults and pediatrics 15, 10, 5 and 1 year(s) old for the heart (organ of interest for this review), urinary bladder wall (organ with the highest absorbed radiation dose), red marrow, testes and ovaries (radiation sensitive organs). The results are presented in Table 4.

Table 4. Absorbed Radiation Doses from 25 mCi of N-13 Ammonia (rem/25 mCi) for Adults and Pediatric Groups 1, 5, 10 and 15 Years Old for the Heart, Urinary Bladder Wall, Red Marrow, Testes and Ovaries

Organ	Adult	15 year	10 year	5 year	1 year
Heart	0.20	0.24	0.38	0.58	1.03
Urinary Bladder wall	0.75	0.98	1.40	2.23	4.25
Red Marrow	0.16	0.20	0.30	0.50	0.93
Testes	0.17	0.18	0.28	0.45	0.88
Ovaries	0.16	0.21	0.33	0.63	1.03

Based on these data, it could be determined whether or not the radiation exposure of these organs, for the 25 mCi intravenous dose of N-13 ammonia, in each of these populations, is acceptable.

In two of the reviewed literature articles^{6,7}, it is indicated that regarding the dosimetry of N-13 ammonia, the critical organ is the wall of the urinary bladder. This is consistent with the findings of the ICRP. One of the two sources⁶ states that in adults, an intravenous injection of 25 mCi of N-13 ammonia is associated with an absorbed radiation dose of 5 mR/mCi (0.005 rem/mCi [i.e., 0.13 rem for a 25 mCi dose]) to the whole body and 51 mR/mCi (0.051 rem/mCi [i.e., 1.28 rem for a 25 mCi dose]) to the [urinary] bladder wall. The urinary bladder absorbed radiation value stated in this literature article is 70% higher the value (0.030 rem/mCi [i.e., 0.75 rem for a dose of 25 mCi]) in Table 3 calculated by this reviewer from the ICRP data presented in Table 2.

(Whole body absorbed radiation data are not provided in the ICRP publication). The other source⁷ states that in adults receiving intravenous doses of N-13 ammonia, the absorbed radiation dose is 18.5 microSv/MBq (0.068 rem/mCi [i.e., 1.70 rem for a 25 mCi dose]) to the urinary bladder wall and 1.5-2.0 microSv/MBq (0.0056-0.0074 rem/mCi [i.e., 0.14-0.19 rem for a 25 mCi dose]) to the whole body. The urinary bladder wall absorbed radiation dose determined in this literature article is 127% higher than the value calculated by this reviewer from ICRP data. These data suggest that differences in dosimetry data determined by different workers in different laboratories could be significant.

III. GENERAL COMMENT

1. Based on the dosimetry data published by the ICRP, the absorbed radiation doses for the highest intravenous N-13 ammonia dose (25 mCi) stated in the reviewed literature articles were calculated, in this review process, for adults and pediatrics 15, 10, 5 and 1 year(s) old for the heart (organ of interest for this review), urinary bladder wall (organ with the highest absorbed radiation dose), red marrow, testes and ovaries (radiation sensitive organs). The results are presented below.

Organ	Adult	15 year	10 year	5 year	1 year
Heart	0.20	0.24	0.38	0.58	1.03
Urinary					
Bladder wall	0.75	0.98	1.40	2.23	4.25
Red Marrow	0.16	0.20	0.30	0.50	0.93
Testes	0.17	0.18	0.28	0.45	0.88
Ovaries	0.16	0.21	0.33	0.63	1.03

These data would be helpful in determining whether or not the levels of radiation exposure for these organs, at this dose level, are acceptable for these populations.

2. The complete dosimetry profile for each of these above age groups is presented in Table 3 (page 7). The dosimetry data for a given intravenous dose of N-13 ammonia can be estimated based on the information presented in this table.

IV. RECOMMENDATION

The literature articles on intravenously administered N-13 ammonia for PET imaging provided by the Agency has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmceutics. Based on the information contained in the literature articles, the effective half-life of N-13 ammonia is 2.21 min, approximately, in human blood. In two of the potential target organs for PET imaging, the myocardium and the brain, its effective half-life values are, respectively, less than 1.67 min and less than 4 seconds. Subsequently, it is considered that for this PET imaging agent, blood or tissue data for pharmacokinetic evaluation would be rather limited and that the pharmacokinetic parameters derived from such data might be of limited value in the assessment of its safety and efficacy. Accordingly, it is considered that for PET (and other procedures) utilizing intravenous N-13 ammonia, pharmacokinetic data need not be required.

The dosimetry information contained in this review would be helpful to the medical officer in making safety decisions that relate to organ absorbed radiation doses from intravenous N-13 ammonia (see General Comments 1 and 2 [page 10]).

Please bring General Comments 1 and 2 (page 10) and the information contained in Table 3 (page 7) to the attention of the reviewing medical officer.

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Reviewer, Division of Pharmaceutical Evaluation II

David Lee, Ph.D.
Team Leader, Division of Pharmaceutical Evaluation II.

V. REFERENCES

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