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SUMMARY OF CONFERENCE ON THE TOXICITY OF CARBON 14

Held at Argonne National Laboratory

January 15-16, 1952

by

A. M. Brues and D. L. Buchanan

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Health and Biology

ARGONNE NATIONAL LABORATORY
P. O. Box 5207
Chicago 80, Illinois

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FOREWORD

The Conference on the Toxicity of Carbon 14 was called at the request of Dr. Shields Warren to exchange such information on the metabolism, toxicity, and measurement of radiocarbon as might have pertinence to the problem of safe laboratory and clinical handling of this isotope.

The invited participants were:

Dr. Austin M. Brues, Argonne National Laboratory, Chairman
Dr. Donald L. Buchanan, Argonne National Laboratory, Vice-Chairman
Dr. Paul C. Aebersold, Isotopes Division, Atomic Energy Commission
Dr. Wallace D. Armstrong, University of Minnesota
Dr. Joseph C. Aub, Massachusetts General Hospital
Dr. Nathaniel I. Berlin, University of California
Dr. William Bloom, University of Chicago
Dr. Walter D. Claus, Atomic Energy Commission
Dr. Cyril L. Comar, University of Tennessee
Dr. Ralph Dorfman, Worcester Foundation for Experimental Biology
Dr. Charles L. Dunham, Atomic Energy Commission
Dr. Robley D. Evans, Massachusetts Institute of Technology
Dr. Miriam P. Finkel, Argonne National Laboratory
Dr. R. Gordon Gould, Los Alamos Scientific Laboratory
Dr. Leon Hellman, Sloan-Kettering Institute for Cancer Research
Dr. Max Kleiber, University of California - College of Agriculture
Dr. Willard F. Libby, University of Chicago
Dr. Arthur Lindenbaum, Argonne National Laboratory
Dr. S. Allan Lough, Atomic Energy Commission
Dr. Leonidas D. Marinelli, Argonne National Laboratory
Dr. Leon L. Miller, University of Rochester
Dr. Karl Z. Morgan, Oak Ridge National Laboratory
Dr. Jesse Perkinson, Oak Ridge Institute of Nuclear Studies
Dr. Oliver Placak, Oak Ridge National Laboratory
Dr. James C. Reid, National Cancer Institute
Dr. John E. Rose, Argonne National Laboratory
Dr. Jack Schubert, Argonne National Laboratory
Dr. Norbert J. Scully, Argonne National Laboratory
Dr. Walton Shreeve, Western Reserve University
Dr. F. Marrott Sinex, Brookhaven National Laboratory

FOREWORD

Dr. Howard E. Skipper, Southern Research Institute
Dr. Robert Steele, Brookhaven National Laboratory
Dr. Bert M. Tolbert, University of California
Dr. N. Edward Tolbert, Atomic Energy Commission
Dr. Shields Warren, Atomic Energy Commission
Dr. M. C. Woods, Oak Ridge National Laboratory

Mr. Akira Nakao and Mrs. Agnes Stroud, Argonne National Laboratory, Recorders.

INTRODUCTION

At the outset of the meeting it was emphasized that the group was brought together to discuss work which had a bearing on the toxicity of C^{14} compounds used either clinically or industrially, and the hope was expressed that the group might be able to reach some conclusions on these matters.

DISCUSSION OF INORGANIC CARBON

The discussion was opened by Dr. Skipper, who reviewed his experiments on the fate of injected bicarbonate.(1) In these experiments, 18 μc (a 50 millicurie man equivalent) was administered to 25 gm mice. In 24 hours 96% was accounted for in expired air and 1.4% in urine. At the end of 9 months over 75% of the retained dose was in the skeleton.

Since the late skeletal deposit shows much more activity in the shafts of long bones, the amount in this mass was determined separately. Between 1 and 2 weeks it was estimated at 0.16 rep/day; between 5 and 6 months at 0.04 rep/day. Thus, the point of greatest activity received a tolerance dose rate, up to and beyond 4 months, when 0.72 μc/gm was administered. Equivalent relative results were obtained when a larger dose (100 μc) was given. Adult steady-state animals were used. The highest bone concentration at 5 months was 3 or 4 times the average bone concentration (Brues and Stroud estimated similarly a factor of 5 by autoradiography, at times up to 2 months).

Dr. Gould mentioned the administration of 0.5 to 1 mc to 5 kilogram monkeys (0.1 - 0.2 μc/gm) and at sacrifice 5 months later no measurable activity was present in bone.

Dr. Armstrong reviewed work done by Dr. Lindenbaum and himself at the University of Minnesota.(2) Six hundred μc of bicarbonate was administered to 600 gm rats (1 μc/gm) by intraperitoneal injection. Total excretion was: 70% in 1 hour, 91% in 3 hours, 95% in 24 hours, and 96% in 4 days. An additional 0.33% was lost in urine and 0.28% in feces on the first day. At sacrifice, 0.051% was in the bone (mainly in inorganic form) and 0.19% in the muscle mass. A total of 97.6% was accounted for.

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(1) Nucleonics, 10, 40, Feb. 1952.

(2) Proc. Soc. Exptl. Biol. Med., 68, 233, 1948
Trans. First Conf. on Metabolic Interrelations, Josiah Macy Jr. Foundation, 1949
J. Biol. Chem., 177, 521, 1949.

By slow, continuous intraperitoneal infusion (1 cc per hour containing 400 μc) a steady state was reached in which 93-94% was excreted constantly in expired air. By 24 hours, the urea specific activity was approximately equal to that of the expired air. Distribution at 116 hours was:

Expired air	94.19%
Urine	3.09
Feces	0.43
G.-I. tract	0.04
Tissues	0.85
Recovery	98.60%

Distribution of tissue activity, where the specific activity of bone carbonate was set at 100, was total bone 12.6, bone protein 3.6, incisor teeth 159.

Dr. Buchanan commented that tissues reach a saturation at various rates, apparently aiming at a plateau.

Dr. Schubert discussed intraperitoneal implantation of 100 mg $CaCO_3$ pellets, mixed with gelatin.(2) The total C^{14} excretion was 1% at 1 day, and 20% at 4 days. After 7 days small amounts of activity were left in the disintegrated pellet (70% had been excreted). The increasing excretion rate may be due to inflammatory reaction or to disintegration of the pellet.

Dr. Gould showed the fate of injected $NaHCO_3$, graphing the total C^{14} retained and the estimated inorganic C^{14} in body fluids, and (by difference) the organic C^{14}. The latter by direct determination reaches a maximum around 5 to 8% at about 1 hour and falls off thereafter. (Similarly, a semi-log plot of the specific activity of expired air can be used to derive the time and amount of maximum sequestration of C^{14} from the bicarbonate pool. Brues and Buchanan obtained similar results in this way.(3))

Dr. Schubert pointed out that bone citric acid is a relatively inert compound as regards C^{14} exchange, and therefore does not account for an appreciable fraction of bone C^{14}.

Dr. Kleiber(4) showed the results of experiments in which cows were injected with C^{14} compounds and the excretion in air and milk measured. After bicarbonate injection, the excretion in expired air is slower than from the mouse, and this rate can be predicted from the respective metabolic rates.

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(3) Cold Spring Harbor Symposium, 13, 52, 1948.

(4) M-4458.

The cow is very efficient in removing carbon from the blood stream into milk; 1% of injected bicarbonate C^{14} appears in milk lactose, and 12% of that in injected acetate appears in milk fat.

Three hour retention of various compounds was shown: carbonate, 22-38%; formate, 68-73%; acetate carboxyl, 52%; acetate methyl, 70-76%; propionate carboxyl, 38%; propionate methyl, 69%; butyrate carboxyl, 40%; butyrate methyl, 66-70%; valerate carboxyl, 49-61%.

Dr. Buchanan[5] showed that the rate of CO_2 excretion by man from injected bicarbonate fell between those for mouse and cow, as predicted from the metabolic rates.

Dr. Hellman showed the early fate of bicarbonate in man; 90% was recovered in 6 hours, of which 2 to 3% was in urine. Urinary urea is not as high in specific activity as the bicarbonate pool; Dr. Buchanan stated similar findings. Dr. Hellman showed that one component of the bicarbonate loss had a time constant of 2 hours or longer.

Dr. Brues[6] discussed experiments of Mrs. Stroud on the acute inhalation of CO_2. That reaching the alveoli of the lung is almost completely in exchange with blood bicarbonate. After a few minutes' inhalation at constant level, a level of expired CO_2 is reached which is somewhat lower. This represents a more or less constant transfer of C^{14} into organic carbon or bone carbonate. This carbon transfer rate was calculated as about one-half as much as across the alveoli. When the inhalation was stopped after 45 minutes the carbon was expired at a much slower rate than that at which it was taken in since the blood bicarbonate at 45 minutes, had reached a specific activity about 50% that of alveolar air. At this time, about one-third of the C^{14} taken in was no longer in the bicarbonate pool.

Activity of various tissues was shown to decline between 1 day and 2 years, approximately as the square root of time. It was pointed out that this logarithmic relation was not necessarily a true one, but was probably a sum of exponentials.

The isotope effect was questioned. Dr. Buchanan[7] kept a closed aquarium for 3 years and found a maximum difference in specific activity of 8% (snail shells higher than growing plant leaves).

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[5] J. Clin. Investigation, 30, 630, 1951.

[6] Federation Proc., 10, 21, 1951.

[7] ANL-4713

Dr. Buchanan summarized work in which animals were kept in atmospheres containing constant levels of $C^{14}O_2$ for periods as long as 6 months.[8] It was found in these experiments that although various adult tissues vary greatly in the initial rate of uptake of isotopic carbon they all tend to approach a constant specific activity which is not exceeded despite continuation of the exposure. Furthermore, this constant level is exceeded but slightly during rapid growth in infant animals. Upon reaching maturity the slight excess of isotope acquired during growth leaves the tissues so that animals raised in the labeled environment contain about the same amount of isotope as adult animals exposed for a long period. The final level of isotope in tissue is governed entirely by the level of isotope in the air and is independent of growth, body size (at least among rats and mice), and total CO_2 concentration of the air. Bone, which contains appreciable inorganic carbon, acquires the highest specific activity of any tissue and may be considered critical (for $C^{14}O_2$ only). From the specific activity found in the bone of animals born and raised in the labeled air it may be calculated that an air level of $C^{14}O_2$ of 30 microcuries per cubic meter can be permitted indefinitely with either adult or growing animals. This level in the air 24 hours per day would ultimately bring the isotope level in bone up to a point where the latter would be getting 0.3 rep per week, but never more.

ORGANIC COMPOUNDS

The discussion of metabolism of organic compounds will be reviewed at somewhat less length; most of the important data will appear in the table.

Dr. Berlin described the metabolism of glycine-2-C^{14} in patients with leukemia and polycythemia.[9] One hundred μc doses were given. The major part of excreted C^{14} was exhaled as CO_2. After 80 days the predominant route of excretion was in urine (but not in urea). From the early expired CO_2 activities 3 rate components (3, 31, and 223 hours) were inferred. Long-term (500 day) retention was around 1 to 2% and the rate of loss suggested a half-time of 2 or more years. Rats after 6 or 7 months retained a measurable amount, but not over 1% (probably less than 0.5%). Human radiation doses after 100 μc glycine fell from 3 mr/day at first to about 0.2 mr/day at around 50 days. Results of norvaline administration to rats were also shown.

Dr. Skipper administered C^{14} formate to mice. Carbon from this purine precursor which is found in the 2 and 8 positions of uric acid, was

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[8] J. Gen. Physiol., 34, 737, 1951.
ANL-4625

[9] J. Clin. Investigation 30, 73, 1951.

largely excreted in urine (20% as CO_2). Autoradiographs, in short term experiments, showed localization in the intestinal crypts, and in the regions of the tubular basement membranes in the testes. There ensued a discussion of the importance of localization of activity in determining cell radiation dosage.

Dr. Miller discussed incorporation of labeled amino acids in animals on various diets, and found comparable rates of disappearance from the amino acids of the circulating blood regardless of the nitrogen balance: he concluded that the state of nitrogen balance did not affect the rate of amino acid incorporation.

Dr. Hellman described clinical administration of 200 μc of methyl-labeled acetate and glycine. After 10 days, 10-15% of the dose remained unexcreted; other confirmatory experiments are shown in Table II. The radiation dose at that time was estimated as less than 1/25 of permissible. C^{14} concentration in bone carbon was less than in liver carbon. Estimation of C^{14} in uric acid showed markedly different time patterns of specific activity between the two compounds. Markedly different metabolic patterns depending on disease states (pernicious anemia or thyroid disease) were shown.

Dr. Gould referred to the behavior of labeled cholesterol, which is not oxidized like acetate. After a few days the blood and liver (5% of the body mass) contain 25% of the activity, a five-fold relative enrichment.

Dr. B. M. Tolbert showed data on the excretion of various compounds not normal to the body: The routes of excretion are strikingly different.

Approximate amounts excreted by various routes are shown in Table I.

Drs. Skipper and Lindenbaum described observations on other unphysiological compounds. Dr. Hellman illustrated the excretion of polyvinylpyrrolidone (65% lost very soon, while 35% remains indefinitely) and dextran (90% excreted, passing through a maximum rate at 2-3 days). Dr. Dorfman described the excretion of steroids in two patients given 800 μc of carboxyl labeled acetate.

Dr. Steele outlined the results of experiments in which uniformly tagged sucrose was fed to mice. About 99% of the C^{14} was excreted in 36 days, 92% as CO_2, the remainder divided equally between urine and feces. At this time, serum carbon showed a lower specific activity than any tissue carbon; and bone specific activity was not exceptional, but appeared to be turning over carbon at a much slower rate. The results of detailed tissue analyses throughout the period of the experiment showed

Table I

Route of Excretion of Various Non-Physiologic Carbon Compounds

(B. M. Tolbert)

Compound	Methadon-2-C^{14}	N-methyl-C^{14} morphine	Dibenz-anthracene 9-C^{14}	N-methyl-C^{14} Demerol	Methoxyl C^{14} Codeine	Stilbami-dine
CO_2	1	male 5 female 1	0	5	50	0
Urine	25	60	0	50	10	40
Feces	60	40	90	10	5	60

that no tissue or organ at any time exceeded 3 times the mean body specific activity at that time. On the assumption that certain small molecule intermediates in instanteneous isotopic equilibrium with expired CO_2 acted as precursors of tissue carbon, an attempt was made to estimate amounts and turnover rates of the tissue carbon fractions, using data for pancreas. An improbable result was obtained, making it clear that the model is inadequate to describe actual events.

THEORETICAL ASPECTS OF TURNOVER

There was some discussion of the use of graphical analysis in determining several rate constants from such data as excretion rates. It was pointed out that while rates and amounts of isotope in compartments may appear obvious where such a curve clearly breaks down into a series of exponential decays, yet even in some simple theoretical models (catenary systems) the true turnover rates and amounts in compartments can be very different and can only be found by successive analyses in the components.[10]

It does appear, however, in spite of the great complexity of time-concentration functions in different compartments, that the specific activity - time product (which has the dimension of total radiation dose) is probably the same throughout all closed steady-state systems.[11] This is illustrated by the parallelism of rates of uptake and of loss in such systems.

TOXICITY STUDIES

Dr. Miriam Finkel presented survival and morbidity data collected on 50 rats and 50 mice each given 500 μc of $NaHC^{14}O_3$ intraperitoneally. These were studied over their entire life span and examined post mortem. Microscopic studies had not been completed but the gross autopsy findings had failed to uncover any significant increase in the incidence of any type of tumor. The survival of the group getting isotopic carbon was slightly but not significantly better than that of the controls.

Dr. Skipper reported his findings on the mortality of Akm mice following 18 μc of $NaHC^{14}O_3$ I.P. The incidence of leukemia in these mice (a susceptible strain) was no different from that of the control group. He also gave labeled formate to mice over a four-month period, a total of 250 μc (780 mc man equivalent), without influence on spontaneous leukemia.

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(10) J. Gen. Physiol., 28, 449, 1945.

(11) ANL-4625

LOW LEVEL COUNTING METHODS

Dr. Libby introduced the problem of counting carbon 14 at specific activity levels where solid $BaCO_3$ techniques were inadequate. He first described the present technique for carbon dating which requires 8-9 gms of carbon. By counting only 300 mg in the same counter about 25% of the net count may be attained. He described a simplified solid counter which can be constructed from plastic sheets and with which fairly routine counts could be made giving good precision (2-3% error) with material 50-100 times the natural radioactive level in an hour or so of counting.

Dr. Tolbert described the ion chamber technique in use at Berkeley and presented a table which compared the relative sensitivity of available counting methods.

There was little difference in the estimated sensitivity of ion chamber measurements, gas counting, and solid counting with pure carbon by the simplified method suggested by Dr. Libby.

Dr. Buchanan called attention to the proportional gas counting method of Bernstein and Ballentine and to recent modifications by Van Slyke, Steele, and Plazin as well as by Buchanan and Nakao.

CONCLUSIONS

In order to make existing retention data comparable a summary was prepared from material presented at the conference, from published work, and from correspondence with participants. This appears in Table II and lists some of the labeled compounds which have been administered as a single dose giving the total body retention at 1 hour, 1 day, 1 week, 1 month, and 1 quarter. These values have largely been obtained by interpolation of plotted data. The "mean per cent retained dose" is simply the integrated level during the 1st day, 1st week, etc. and from this one may obtain the dose (in μc per gm) which will give the accepted tolerance dose of radiation (0.3 rep per week) over the 1st day, 1st week, etc. Finally a column is included which gives the equivalent dose to a 70 kg. man. The final two columns of course imply uniform distribution, and do not take into account the metabolic rates of different species, which determine the rate of discharge of the bicarbonate pool in expired air. It will be noted that in the case of several compounds, data are available only for retention at the end of 1 hour or 1 day. There are, naturally, pitfalls in extrapolating such data to much longer periods.

The present tolerance dose is expressed as the integrated dosage over 1 week (0.3 rep). If integration may be done over 3 months, the permissible amounts of compounds discussed here become substantially larger.

Table II

Resumé of Carbon 14 Retention

No.	Compound	Animal	Route	% Dose retained at					Mean % retained during 1st					μc/g to give tolerance during 1st					Man equivalent dose mc					Principal Investigator
				1 hr.	1 day	1 wk.	1 mo.	3 mo.	hr.	day	wk.	mo.	3 mo.	hr.	day	wk.	mo.	3 mo.	hr.	day	wk.	mo.	3 mo.	
1.	$NaHC^{14}O_3$	mice (25 g)	IP	7.0	1.4	0.6	0.13	0.12	22.7	4.1	1.3	0.5	0.25	0.066	0.37	1.2	3.0	6.0	4.6	26.0	84.0	210	420	H. E. Skipper
2.	$Na_2C^{14}O_3$	rats (624-472 g)	IP	29	4.6	1.0	0.5	-	55	8.2	3.6	1.4	-	0.027	0.18	0.42	1.1	-	1.9	13	29	77	-	W. D. Armstrong J. Schubert
2a.	$NaHC^{14}O_3$	rats (120-140 g)	IP	15	-	-	-	-	38	-	-	-	-	0.039	-	-	-	-	2.7	-	-	-	-	R. G. Gould
3.	$NaHC^{14}O_3$	human (55-84 kg)	IV	25	-	-	-	-	49	-	-	-	-	0.030	-	-	-	-	2.1	-	-	-	-	D. L. Buchanan
4.	$NaHC^{14}O_3$	cow	IV	37	-	-	-	-	68	-	-	-	-	0.022	-	-	-	-	1.5	-	-	-	-	M. Kleiber
5.	Sucrose (uniform labeling)	mice (25 g)	oral	80	15	2.0	0.6	-	90	37	10	3.2	-	0.017	0.041	0.15	0.47	-	1.2	2.9	10.5	33.0	-	R. Steele
6.	$C^{14}H_2NH_2COOH$	human	IV	~100	45	20	9	6	100	75	40	20	10	0.015	0.023	0.039	0.075	0.15	1.0	1.6	2.7	5.3	10.0	N. I. Berlin
7.	$NaC^{14}OOCH_3$	human	IV	83	35	-	-	-	93	44	-	-	-	0.018	0.034	-	-	-	1.3	2.4	-	-	-	W. W. Shreeve
8.	$C^{14}H_2NH_2COOH$	mice	IV	-	76	40	12	-	-	85	57	30	-	-	0.018	0.026	0.050	-	-	1.3	1.8	3.5	-	G. Nardi
9.	$CH_3C^{14}OOH$	rats (120-140 g)	IP	-	35	-	-	-	-	63	-	-	-	-	0.024	-	-	-	-	1.7	-	-	-	R. G. Gould
10.	$C^{14}OOHCH_2C^{14}OOH$	rats (120-140 g)	IP	-	45	-	-	-	-	87	-	-	-	-	0.017	-	-	-	-	1.2	-	-	-	R. G. Gould
11.	$C_2H_5OOC^{14}NH_2$	mice (25 g)	IP	93	1.3	<1.3	-	-	96	37	< 6	-	-	0.015	0.044	>0.25	-	-	1.1	3.1	17.5	-	-	H. E. Skipper
12.	$CH_3C^{14}H_2OOCNH_2$	mice (25 g)	IP	96	6.2	<6.2	-	-	98	40	<10	-	-	0.015	0.038	>0.15	-	-	1.1	2.7	>10.5	-	-	H. E. Skipper
13.	$CH_3C^{14}H_2OH$	mice (25 g)	IP	38	6.2	<6.2	-	-	74	12	<12	-	-	0.020	0.13	>0.19	-	-	1.4	9.1	>13.3	-	-	H. E. Skipper
14.	8-Azoguanine (Guanazolo)	mice (25 g)	IP	-	8.2	-	-	-	-	<54	-	-	-	-	>0.028	-	-	-	-	>2.0	-	-	-	L. L. Bennett
15.	$CH_3C^{14}OOH$	cow	IV	87	-	-	-	-	93	-	-	-	-	0.016	-	-	-	-	1.1	-	-	-	-	M. Kleiber
16.	$C^{14}H_3COOH$	cow	IV	83	-	-	-	-	91	-	-	-	-	0.016	-	-	-	-	1.1	-	-	-	-	M. Kleiber
17.	$CH_3CH_2CH_2C^{14}OOH$	cow	IV	70	-	-	-	-	83	-	-	-	-	0.018	-	-	-	-	1.3	-	-	-	-	M. Kleiber
18.	$CH_3CH_2C^{14}OOH$	cow	IV	58	-	-	-	-	72	-	-	-	-	0.021	-	-	-	-	1.5	-	-	-	-	M. Kleiber
19.	$NaHC^{14}O_3$	cow	IV	53	-	-	-	-	69	-	-	-	-	0.022	-	-	-	-	1.6	-	-	-	-	M. Kleiber
20.	Norvaline^{-3} C^{14}	rat	IP	-	55	40	20	8	-	65	49	33	19	-	0.013	0.031	0.045	0.079	-	1.6	2.2	3.2	5.5	N. I. Berlin
21.	Acetate	man	IV	-	50	20	5	-	-	60	35	15	-	-	0.025	0.043	0.10	-	-	1.8	3.0	7.0	-	L. Hellman
22.	Glycine	man	IV	-	50	20	5	-	-	60	35	15	-	-	0.025	0.043	0.10	-	-	1.8	3.0	7.0	-	L. Hellman
23.	Bicarbonate	man	IV	-	<10	-	-	-	-	<50	-	-	-	-	>0.030	-	-	-	-	>2.1	-	-	-	L. Hellman
24.	Methionine	man	IV	-	65	20	-	-	-	75	38	-	-	-	0.020	0.039	-	-	-	1.4	2.7	-	-	L. Hellman
25.	Urea	man	IV	-	< 5	-	-	-	-	<50	-	-	-	-	>0.030	-	-	-	-	>2.1	-	-	-	L. Hellman
26.	Nicotinic Acid Nicotinamide (Carbonyl Labeled)	mice	IP	-	2	<1	-	-	-	40	7	-	-	-	0.038	0.21	-	-	-	2.7	14.7	-	-	L. Roth

Of the compounds surveyed, glycine showed the highest retention values, but there seems no serious reason to believe that this compound is unsafe in an adult human dose of 1 mc.

There was general agreement that it is justifiable to integrate radiation doses over a 3-month or 13-week period (equivalent to 3.9 rep in this time).

There was agreement that in the case of new compounds, experimental studies of long-term accumulation should precede approval for human use. It was also agreed that sensitive counting methods were desirable in human studies as a means of reducing the necessary dose, but there was no general agreement as to how far one was bound to go in time and expense to accomplish this.

Diagnostic procedures justify the use of larger amounts than other experimental procedures. At the present time, even terminal patients do not receive a tolerance dose of any compound without special permission.

No discontinuities in distribution of any compounds have been reported such that a single area receives more than 5 or 10 times the average total body dose. None of the organic compounds have shown the high relative skeletal concentration seen with bicarbonate; in this case Skipper's empirical observations on adult mice seem pertinent.

The deposition of carbonate in growing bone, and of compounds that may selectively irradiate the gonads, require special consideration.

Regarding continuous inhalation of $C^{14}O_2$, the picture seems clear as a result of experimental studies. An air level of 30 $\mu\mu c/cc$ will never cause the tolerance level to be exceeded. This level implies a specific activity between 0.15 and 0.2 $\mu c/mg$ in the carbon of air which has the normal composition. Intermittent exposure, say one-fourth of the time (42 hours/week) should make it permissible to raise the concentration by the same factor.

One hundred and fifty mc of C^{14} in an acute accidental inhalation would probably not exceed the permissible dose. Forty mc would give a standard man 1 rep over his lifetime. (The acute lethal dose would probably exceed 100 C.)

The question of waste disposal was brought up; it was generally assumed that almost all of the material, in whatever form, would eventually go off as CO_2, so that the eventual concentration of C^{14} need not be a matter for concern.

This report was prepared with the assistance of notes taken by Mr. Nakao and Mrs. Stroud. Several of the participants contributed graphical or tabulated data which have been incorporated into the table. The conclusions and recommendations were prepared from a transcript of discussions by Drs. Armstrong, Berlin, Buchanan, Claus, Marinelli, and B. Tolbert.