A study of the stability and radiochemical purity of some radiopharmaceuticals.
1. Calculations of absorbed radiation energy

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SUMMARY

The radiation energy absorbed in solutions of phosphorus-32, iodine-125 and -131, mercury-197 and -203 was calculated and tabulated for various time of storage. The influence of geometrical shape of solutions was also evaluated. An experimental verification of calculations was carried out for solutions of iodine-131, the good agreement was obtained. The possibilities and limitations of the use of external gamma irradiation for estimating the self-radiation effect were discussed.

INTRODUCTION.

The purity and especially the radiochemical purity is one of the basic demand on radiopharmaceuticals. Radiochemical impurity at the percent level can sometimes lead to wrong diagnostic result or cause a serious injury for organ other than that which is to be therapeutically treated. The decomposition which occurs in radiopharmaceuticals on storage owing to the effects of their own radiation may be a serious source of impurities, additional to the insufficient purification processes applied in their production and other "normal" chemical reactions not connected with the radiation. The present knowledge of the self-irradiation decomposition of labelled compounds was recently reviewed [1-3].

The stability of a given radiopharmaceutical can be studied either (i) by the estimation of an overall decomposition under the stated conditions of storage, or (ii) by estimation of the contributions of temperature, light, radiation, etc., simultaneously. The second mentioned method is based on the simplyfying assumption that the effects of all processes are additive.

The processes occuring in radiopharmaceuticals during their storage can be classified on

(i)   radiation processes,

(ii) chemical processes, especially hydrolysis and oxidation; these processes are usually temperature dependent,

(iii) photochemical processes; can be avoided by keeping the preparation in the darkness.

Radiation processes were classified by Bayly and Weigel [4]. Most radiopharmaceuticals are supplied in aqueous solution, for our purposes it seems to be therefore reasonable to differentiate two stages of radiation decomposition :

(A) The radioactive isotope disintegrates independently of its chemical state. The emitted ionizing radiation is partially absorbed in the solution. The total energy absorbed in the solution in a time interval depends on the radioactive concentration (mCi/ml), energy and type of emitted radiation, total volume and geometrical shape of the solution.

(B) The solution of the radiopharmaceutical is decomposed due to the action of ionizing radiation. The amount of decomposition of the radiopharmaceutical is a function of total absorbed energy (radiation dose) and the radiation yield of decomposition ($G_{(-M)}$ value). The radiation yield of decomposition depends on the concentration of the radiopharmaceutical, on the presence of other substances (including dissolved oxygen), on the intensity of radiation (dose rate), and in some cases on the linear energy transfer (L. E. T.).

The processes described in the paragraph (A) are common for all radiopharmaceuticals containing the same radioactive isotope. If the amount of absorbed energy is known, it is easy to simulate the self-radiation by an external radiation, to obtain the same effect. This is the way how to accelerate decomposition experiments. The accelerated experiments are well known and often used in studying the stability of nonradioactive pharmaceuticals [5, 6]. However, the applicability of this method is limited if the radiation decomposition yield markedly depends on the dose rate and/or on L. E. T.; this will be discussed later.

1. — CALCULATION OF ABSORBED ENERGY.

The absorbed energy calculations require the knowledge of (a) the number of disintegrations per time interval in the volume unit, (b) the total energy release per disintegration, (c) the modes of absorption of various kinds of radiation in the medium, (d) the geometrical shape of absorbing medium.

The energy absorbed from the disintegration of phosphorus ^{32}P, iodine ^{125}I and ^{131}I, and mercury ^{197}Hg and ^{203}Hg were calculated using the following presumptions and terms.

The initial radioactive concentration of each radioactive isotope is consi-dered to be 1 mCi per ml.

The cylinder having 2 cm in diameter and high 1 cm (volume 3.14 ml) is chosen as the geometrical unit for the shape of absorbing medium; absorp-tion of ionizing radiation in any other cylinder is compared with this unit.

The absorbed energy is expressed in electrovolts per millilitre (eV/ml). The absorbing medium is considered to be pure water.

The physical properties of the above-mentioned radioisotopes, used in calculations are shown in Table 1.

TABLE 1. Physical properties of some radioisotopes.

Radio-isotope	Half-life (days)	Beta energy			Gamma energy		Linear energy abs. coeff. μ_a	Total spec. gamma-ray const., Γ
		max. (MeV)	%	mean[a] (MeV)	MeV	%		
[32]P	14.3	1.71	100	0.696[c]				
[125]I	60.2			0.0208[d]	0.0274[d]	112.6[d]	0.170	1.23[d]
					0.0311[d]	24.2[d]	0.125	
					0.0354[d]	7 [d]	0.085	
[131]I	8.06	0.250	2.8	0.189[c]	0.080	2.2	0.025	2.3[e]
		0.335	9.3		0.163	0.7	0.029	
		0.608	87.2		0.284	5.3	0.033	
		0.815	0.7		0.364	80.0	0.034	
					0.637	9.0	0.033	
					0.722	3.0	0.032	
[197]Hg	2.7			0.079[d]	0.0682[d]	57[d]	0.027	0.31[d]
					0.0772[d]	20[d]	0.025	
					0.0788[d]	18[d]	0.025	
[203]Hg	47	0.208	100	0.099[d]	0.772[d]	9.1[d]	0.026	1.20[d]
					0.0824[d]	3.6[d]	0.025	
					0.279[d]	81.5[d]	0.033	

[a] including conversion electrons; [b] Ref. (7); [c] Ref. (8); [d] Ref. (9); [e] Ref. (10). Other nuclear constants according Ref. (11).

1.1. — Calculation of absorbed energy from beta particles, electron capture and internal conversion.

Calculations were carried out according to the principles of Loevinger et al. [12]. At first, the effective absorption coefficient of beta particles was found for phosphorus-32, iodine-131 and mercury-203 (using the Fig. 7 of

TABLE 2. The values used in calculation of absorbed energy from beta particles. For symbols see the text.

Radio-isotope	Effective abs. coeff. cm²/g	x cm	N	Total energy[a] eV/sec
^{32}P	10	0.3	0.873	2.57×10^{13}
^{125}I	—	—	—	7.7×10^{11}
^{131}I	40	0.075	0.887	7.0×10^{12}
^{197}Hg	—	—	—	2.94×10^{12}
^{203}Hg	200	0.015	0.887	3.67×10^{12}

a) Total energy of beta particles (including the electron capture and internal conversion) released by one milicurie of radioisotope per second.

reference 12). By means of this value (see Table 2) the thickness of layer (x) in which the absorption is incomplete was estimated. Then the energy absorbed in this layer was calculated (using the values of the Fig. 14 of reference 12) and expressed as a fraction of complete absorption (N). Then the volume of total absorption [$\pi (r - x)^2 (h - 2x)$] was calculated for a cylinder of radius r and of height h. The ratio of volume of total absorption to the whole volume was denoted F. The total percentage of absorbed energy, Pβ is :

$$P\beta = 100 F + 100(1 - F)N.$$

Using the value Pβ and the total energy of beta particles and electrons released in the decay of 1 mCi of a given radioisotope, the energy absorbed in cylinders of various sizes was calculated.

The results obtained showed that even for the smallest cylinde ($r = 0.5$ cm, $h = 1$ cm) up to 95.5 and 99.0 percent of the energy of emitted electrons was absorbed in the case of iodine-131 and mercury-203, respectively. The electron radiation from mercury-197 and iodine-125 was therefore considered to be completely absorbed in all cylinders taken into consideration.

1.2. — *Calculation of absorbed energy from gamma radiation.*

For the calculation of the fraction of gamma radiation absorbed in the solution of radioisotope we used the revised average geometric factors $\bar{g}$, recalculated recently by Focht et al. [13] for cylinders containing a uniform distribution of gamma-ray emitter; the necessary values were obtained by graphical interpolation, Focht et al. calculated the $\bar{g}$ values for the linear energy absorption coefficient $\mu_a = 0.028$. As it is seen from the Table 1, the values of μ_a for the individual radioisotopes (except the iodine-125) are not too different from the above-mentioned value. Due to the fact, that only a very small fraction of gamma radiation is absorbed in cylinders under study,

the error caused by neglecting the differences in μ_a does not influence seriously the value of total beta-gamma absorbed energy.

The absorbed gamma energy $R\gamma$ was calculated using the equation [14]

$$R\gamma \text{ (eV/g/sec)} = C\rho\Gamma \bar{g} \times 98 \frac{6.24 \times 10^{11}}{3.6 \times 10^3},$$

where C denotes the radioactive concentration of uniformly distributed radioisotope, ρ denotes the density of water, and Γ denotes the specific gamma-ray constant (roentgens cm^2/mCi hr). The value of 98 ergs was considered to be equivalent to the dose of one roentgen.

The absorbed energy of gamma-rays of iodine-125 was calculated using the table for self-absorption of gamma rays in cylindrical sources [15], the graphical interpolation was used. The obtained values were multiplied by a factor of 1.3, to achieve better accordance with the recent results of Ellett et al [16].

1.3. — Calculation of the total absorbed energy.

The total absorbed energy was acquired by summing up the contributions of beta and gamma radiation Several results are shown in Table 3, to illustrate the magnitude pf contributions of beta and gamma-rays. The resulting values (in eV/ml/sec) were then expressed as a fraction of the value corresponding to the cylinder having 2 cm in diameter and a height of 1 cm (geometrical unit), which was chosen as an arbitrary unit; the results are shown in Figure 1.

The values of absorbed energy for various storage times were obtained by integrating in a usual way, using the half-lives presented in Table 1. The results, expressed in eV/ml, are shown in Table 4 and 5.

To calculate the energy absorbed in one mililitre of solution of the radiopharmaceutical for a particular time, the appropriate value from the Table 4

TABLE 3. The energy absorbed in one mililitre of solution (eV/ml/sec) in cylinders of various heights (diameter 2 cm) with uniformly distributed iodine-131 (1 mCi/ml).

	height of cylinder, cm			
	1	2	3	4
beta energy[a]	6.79	6.83	6.85	6.86
gamma energy[a]	0.15	0.25	0.34	0.39
sum[a]	6.94	7.08	7.19	7.25

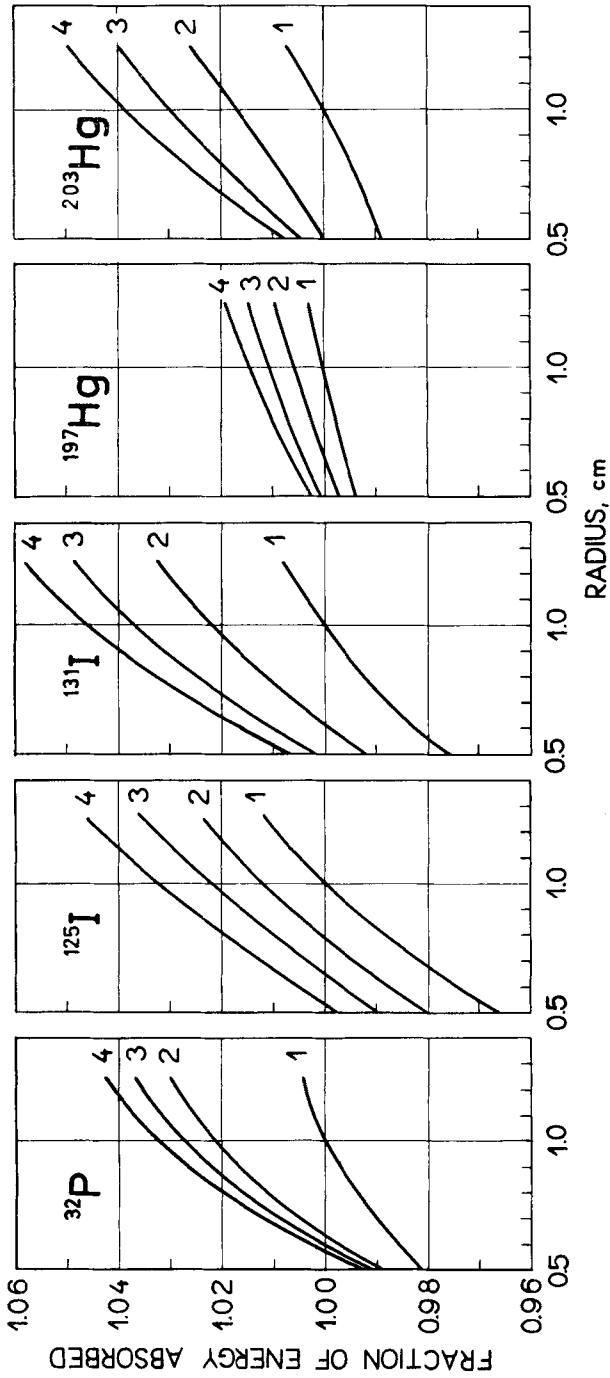[a] All numbers must be multiplied by a factor 10^{12}.

FIG. 1. The dependence of total absorbed energy on the geometrical shape of absorbing medium. The cylinder with parameters $r = 1$ and $h = 1$ is considered as a unit. The numbers attached to the curves indicate the respective heights of cylinders in cm.

TABLE 4. The absorbed energy (in 10^{17} eV/ml) in solutions having the initial radioactive concentration of 1 mCi/ml; the values refer to the geometrical unit.

Radio-isotope	days of storage														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
^{197}Hg	2.25	3.99	5.33	6.37	7.17	7.80	8.28	8.65	8.94	9.17	9.34	9.46	9.58	9.65	9.72
^{131}I	5.7	11.0	15.8	20.2	24.4	28.0	31.5	34.6	37.5	40.2	42.6	44.7	46.9	48.6	50.4
^{32}P	19.5	37.8	55.5	72.4	88.4	104	118	132	145	159	170	181	192	202	212

TABLE 5. The absorbed energy (in 10^{17} eV/ml) in solutions having the initial radioactive concentration of 1 mCi/ml; the values refer to the geometrical unit.

Radio-isotope	days of storage														
	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
^{203}Hg	3.25	12.4	24.1	35.2	45.6	55.6	64.7	73.4	81.6	89.5	96.6	104	110	116	122	127
^{125}I	0.64	2.5	4.9	7.2	9.4	11.4	13.4	15.3	17.1	18.9	20.5	22.1	23.6	25.1	26.4	27.8

or 5 must be multiplied by the actual initial radioactive concentration of the preparation. Then the correction for different geometrical dimensions can be applied. For example, the total energy absorbed in one mililitre of solution of phosphorus-32 (having the initial radioactive concentration 5 mCi/ml) during the storage for ten days in a vial ($r = 1$ cm, $h = 4$ cm) is :

$$5 \times 145 \times 1.03 \times 10^{17} \, eV/ml = 7.46 \times 10^{19} \, eV/ml.$$

2. — EXPERIMENTAL ESTIMATION OF ABSORBED ENERGY IN IODINE-131 SOLUTIONS.

Water saturated with chloroform [17] was chosen as a chemical dosimeter for the estimation of the absorbed dose in iodine-131 solutions.

The iodine-131 solution was prepared by trapping the vapours of carrier-free iodine-131 into 0.01 N solution of sodium hydroxide. After the addition of potassium iodide carrier (to prevent the loss of activity during the storage)
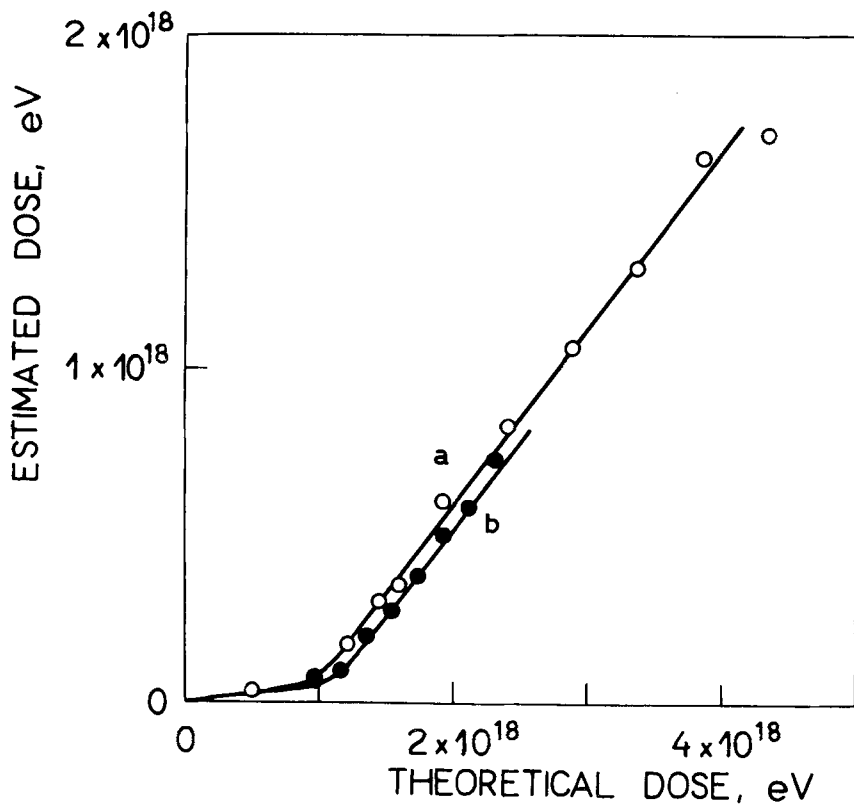

FIG. 2. The plot of theoretical versus estimated radiation dose for chloroform dosimeter with the concentration of added potassium iodide of (a)1.92 × 10⁻⁴ M and (b) 2.22 × 10⁻⁴ M.

the solution was carefully neutralized with hydrochloric acid and agitated with the calculated amount of purified [17] chloroform. Then this solution was transferred into cylindrical ampoules of various sizes. All ampoules (borosilicate glass) were boiled with concentrated chromic mixture and several times with distilled water before use. The ampoules were stoppered with polythene. The gamma-activity in each ampoule was measured using a calibrated 4 ionization chamber. The initial radioactive concentrations of iodine-131 in dosimeter varied from 0.7 to 1.2 mCi/ml. The ampoules were opened after several days of storage in dark and the hydrochloric acid liberated by the radiation was titrated by 0.001 N solution of sodium hydroxide, using bromcresol purple as an indicator. The zero-time value was estimated immediately after the preparation of dosimetric solution. From these values the absorbed dose was calculated using the G_{HCl} value of 25.0 and corrected according to the calibrating curves (Fig. 2). The calibrating curves were obtained from the solutions of non-radioactive potassium iodide saturated with chloroform and irradiated with cobalt ^{60}Co gamma-rays under well defined conditions (each irradiation position was calibrated by a Fricke dosimeter).

The independence of the radiation yield of hydrochloric acid in the system aqueous solution of potassium iodide-chloroform on the quantity of added sodium chloride and on the dose rate was also established by means of external gamma-irradiation.

Table 6 shows both values of absorbed radiation energy of iodine-131, calculated and experimentaly determined, for cylinders of various sizes.

3. — Discussion.

The calculations performed show that in geometrical shapes under study the predominant part of absorbed radiation energy comes from beta particles and conversion electrons.

Some doubts can exist about the use of universal function (instead of the actual one for each individual radioisotope) in calculating the absorption of beta particles in the surface layer. Fortunately, the calculations showed that the deviation even minus 10 percent in evaluating the fraction of the incomplete absorption can lower the total result to only 2-3 percent foi the smallest cylinders. Owing to the effect of back-scattering of electrons from the glass walls, the percentage of absoibed beta particles in the surface layer will be rather highei than that predicted by calculation used. So, the danger of overestimating the final values is minimized.

There were two possibilities in calculating the gamma-ray contributions [13, 15]. We prefer the tables of Focht et al., while the tables of Kovalev [15] give higher values. This difference seems not to be serious for our purposes, due to a very small influence of gamma-rays on the final value of absorbed

energy. In the case of iodine-125 even the method used [15] gave low values as compared with the values of Ellett *et al.* [16] extrapolated to our geometrical dimensions. To minimize this difference we applied a correction factor. The contribution of gamma-rays to the final value of absorbed energy does not exceed 15 percent in the case of iodine-125, being smaller for other radio-isotopes.

Most radiopharmaceuticals are packed in standardized multidose glass vials the diameter of which is approximately 2 cm [18]. This was the reason for the choice of our geometrical unit. The Figure 1 shows, that the fraction of absorbed energy increases only moderately with increasing both radius and height of cylinders.

The chemical dosimetry seemed to be the most convenient method for the experimental estimation of the total absorbed dose. The presence of iodides influences the radiation yield of Fricke dosimeter and therefore the water-chloroform system was prefered, having in addition higher radiation yield. Unfortunately, a strong dependence of the hydrochloric acid radiation yield on the concentration of added potassium iodide has been found; the G_{HCl} value decreases exponentialy with increasing iodide concentration. In the presence of iodides the G_{HCl} value changes also with increasing radiation dose, therefore the calibration curves were used. The independence of G_{HCl} value on the dose rate was proved especially with respect to the doubts of Allen [19a] concerning this phenomenon; no differences in G_{HCl} were found within the limits of dose rate values 0.73×10^{16} to 6.2×10^{16} eV/ml/min.

The agreement of calculated and experimentally established values of absorbed radiation energy of iodine-131 (Table 6) is very good, bearing in mind all possible sources of error, particularly the activity measurement. Light differences exist — the experimental values are lower for the lowest cylinders and higher for the highest cylinders as compared with the calculated ones.

Moreover, this agreement of experimental and calculated values shows the actual accordance of radiolytical and self-radiolytical yields, which is still the topic of discussion or doubts [1]. This doubts could be justified in systems for which the knowledge of radiation yields as a function of L. E. T. is missing, which is generaly not the case for aqueous solutions. In the interval of L. E. T. 0.01 to 0.2 eV/Å, which is characteristic for the most beta or beta-gamma emitters (with the exception of tritium), the changes in radiation yields of various radicals arising in radiolysed water do not exceed 25 percent of their value [19b]. Some other cause must therefore account for the discrepancies, for example the presence of small quantity of protective compound or the difference in dose rate applied. Especially, this second reason could be serious and the dependence or inependence of the radiation yields on the dose rate have to be proved; the dose rate during self-decomposition is often by one or two orders lower than that used in external irradiation.

The accelerated irradiation experiments have been used for many years,

TABLE 6. The comparison of calculated and estimated values of radiation energy absorbed in solution of iodine-131.

radius cm		height, cm				
		1	2	3	4	5
0.46	a	2.14	2.17			
	b	2.05	2.20			
	c	95.8	101.3			
0.55	a	2.15	2.19	2.21	2.22	
	b	1.90	2.39	2.33	2.44	
	c	88.6	109.2	105.3	109.8	
0.69	a	2.17	2.21	2.24		
	b	1.86	2.23	2.43		
	c	86.1	101.0	108.7		
0.79	a	2.18		2.26		2.27
	b	2.11		2.14		2.48
	c	96.8		94.8		109.3

(a) Calculated; (b) estimated radiation dose in eV/ml; each value must be multiplied by a factor of 10^{18}. (c) The percentage of the estimated value, considering the calculated value as 100 percent.

particularly for qualitative purposes. The investigation of labelled cyano-cobalamin [20] can serve as an example of semi-quantitative study. The accelerated irradiation experiments give the possibility to obtain the information of different influences (pH of solution, protective effects, etc.) on the system under study in much shorter time and with much lower activities; the activity in such experiments serves only for analytical purposes. The external irradiation enables us to observe the decomposition to higher extent making such studies more precise as compared with self-irradiation experiments. We try to use this technique for the study of stability of some radiopharmaceuticals labelled with radioisotopes of iodine or mercury, the results will be published in the following articles.

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