BioMetals 1993, **6**, 163–170

Some biochemical aspects of the protective effect of strontium chloride on γ-irradiated rats

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Received 1 September 1992; accepted for publication 14 January 1993

The effect of treatment with $SrCl_2$ (10 mg 100 g^{-1}) on rats 15 min prior to whole body γ-irradiation (7.5 Gy) was studied. The hazardous effects of irradiation were greatly corrected in the treated group. The hyperglycemic effect and liver glycogen accumulation in the untreated group decreased to normal level. The enzymatic activities of serum alkaline phosphatase, alanine and aspartate aminotransferases, and lactate dehydrogenase were greatly affected, showing insignificant changes in the treated group of animals. Life span calculated on 50% survival was also significantly elongated by 36.3%. These results show the potentiality of $SrCl_2$ as a radioprotective agent. A proposed mechanism is discussed.

Keywords: γ-irradiation, radioprotector, rats, strontium chloride

Introduction

The great technical advancement in the application of nuclear power as an alternative source of energy has created many disastrous and unexpected hazardous problems. The health and social problems have drawn attention to the importance of protection from irradiation dangers (IAEA 1986). These dangers range from complete and total destruction of life to diseases that lead to death even after many years of exposure. Therefore, a search for other forms of such tools which could reduce radiation hazards or induce certain protection against radiation diseases is urgently needed.

The well-known character of certain heavy elements in affecting chelation has been thought to play a possible role in protective measures against radiation syndrome (Roushdy & Mansour 1982, Morgan *et al.* 1985).

Due to the presence of long-lived radioactive isotopes, several studies have been conducted on such elements. It has been reported that the pathway of elemental strontium through the human body follows that of calcium; about 99% of its intake being excreted in the feces and urine (Oser 1979).

We therefore studied the effect of strontium chloride ($SrCl_2 \cdot 6H_2O$) as a newly proposed compound on irradiated rats and some important parameters were investigated.

Materials and methods

Experimental animals

Male Swiss albino rats (National Organization for Drug Control Research) with a mean weight of 100 ± 5 g were housed in plastic cages (four per cage) under standard conditions. The animals were provided with their daily feeding requirements using concentrate pellets (Ministry of Agriculture Research Laboratory). The concentrate was enriched with salt and vitamin mixtures. The animals had free access to water.

Irradiation process

Before whole body irradiation, the animals were fasted for 12 h. A Gamma cell 40 (caesium-137) irradiation unit (Atomic Energy of Canada Limited) was used. The dose rate was 1.404 rad s^{-1} calculated using a Frick dosimeter (Attix 1970). The caesium-137 double-encapsulated source was maintained within two cylindrical sliding drawers, above and below the sample cavity. A plastic sample tray with lid and supports surrounded by ventilation holes

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along its side which align with ventilation parts through the main shield was used.

Strontium chloride hexahydrate (99.9%) was supplied from Aldrich Chemical Co.

Life span experiment

Forty rats of the same sex and with a mean weight of 100 ± 5 g were equally divided into two groups (20 rats each).

Group 1 (Ir): rats were injected intraperitoneally with sterile distilled water (0.5 ml) then subjected to γ-irradiation at a dose of 7.5 Gy.

Group 2. ($SrCl_2$-Ir): rats were injected intraperitoneally with sterile $SrCl_2$ solution (10 mg 100 g body weight), 15–30 min prior to γ-irradiation at the same dose.

Individual body weight was recorded on days 5, 7 and 10. The whole experimental period was 15 days.

Experimental plan

A total number of 140 rats weighing 100 ± 5 g were divided into four groups according to the following scheme:

Group I (NC): 30 normal rats served as a normal control group.

Group II (Ir): 40 rats were subjected to whole γ-irradiation of 7.5 Gy (about 750 rad) and served as an irradiated group.

Group III ($SrCl_2$): 30 rats received a single intraperitoneal injection of $SrCl_2$ solution (10 mg 100 g body weight^{-1}) and served as a non-irradiated treated group.

Group IV ($SrCl_2$-Ir): 40 rats were injected intraperitoneally with $SrCl_2$, 15–30 min pre-whole body γ-irradiation and served as an irradiated treated group.

Six animals of each group were sacrificed on days 1, 3, 7 and 10 post start of the experiment for serum and liver tissue studies.

Blood sampling and preparation of liver homogenate

Animals were sacrificed after being lightly ether anesthetized. Blood samples were withdrawn by heart puncture using plastic disposable syringes. Blood serum was kept at −20 °C until assayed. Livers were dissected, freed from adhering non-hepatic tissue, blotted dry, weighed and then divided into two weighed pieces. One portion was placed in a test tube containing 30% KOH for glycogen determination. The other part of the liver tissue was homogenized in glass distilled water (1:5 w/v). Tissue homogenates were kept frozen at −20 °C until analysis.

Biological assays

Serum glucose was assayed according to Morin & Jerome (1973). Serum and liver homogenates were subjected to the determination of lactate dehydrogenase (LDH) (Wootton & Freeman 1982), alkaline phosphatase (ALP) (Belfield & Goldberg 1971), and alanine and aspartate aminotransferases (ALT and AST) (Reitman & Frankel 1957). Liver glycogen content was assessed according to the method of Hassid & Abraham (1957).

Statistical analysis

For statistical evaluation, group means were compared using Student's t-test. The calculations were carried out according to Snedecor & Cochran (1982).

Results and discussion

The effect of $SrCl_2$ on the life span of γ-irradiated rats (7.5 Gy) is shown in Table 1. The elongation of life span in animals of Group 2 ($SrCl_2$-Ir) was significantly increased by 36.6%. In addition, no deaths were recorded during the first week of the experiment as compared with 40% deaths in the same period in untreated irradiated animals. The latent period was also highly affected as the animals of Group 2 ($SrCl_2$-Ir) recorded a remarkable increase in this period, which amounted to 63.3% compared with 18.2% for Group 1 (Ir). It is also to be emphasized that on the basis of 50% mortality on day 11 for Group 2, this percentage is recorded as 100% in Group 1 for the same period. Covelli *et al.* (1988) reported that the main cause of death for irradiated rats is the induction of solid tumors. It has been reported that life shortening appeared to be a linear function of dose. Data recorded on causes of death show that malignant tumors, such as leukemias, thymic lymphomas and non-cancerous late degenerative changes in lung, were the principal cause of life shortening after a high single γ exposure (Maisin *et al.* 1988). Thus, it appears that this kind of treatment not only elongated the life span but also exhibited better health in the animals of the treated group as shown by the extension of the latent period which potentiates two important goals realized by such treatment.

Table 2 shows the ratio of liver wet weight to body weight in all tested rats. The mean normal ratio was found to be 0.04 ± 0.005, which is in line with the findings of Litterst *et al.* (1972) using a different strain (male Osborne-Mendal rats). This ratio is known to increase in γ-irradiated rats (Kilberg & Neukaus 1972, Sobocinski & Altman 1976), which is the case in our study. The increasing rate in this ratio starts with 25% on day 1 and ending with 45% by day 10, by which 90% mortality is reported.

The effect of $SrCl_2$ *per se* showed non-significant changes while the ratio in Group IV ($SrCl_2$-Ir) showed the most striking results as non-significant changes continued up to day 7, after which the overwhelming lethal dose of γ-irradiation is re-

Table 1. Effect of $SrCl_2$ treatment on mortality (%) of γ-irradiated rats

Group 1			Day post-irradiation	Group 2		
mean body wt (g)	no. of deaths	mortality (%)		mean body wt (g)	no. of deaths	mortality (%)
100 ± 5.00	0	0	1	100 ± 5.00	0	0
	0	0	2		0	0
	1	5	3		0	0
	1	10	4		0	0
91 ± 2.90	2	20	5	95 ± 2.800	0	0
	2	30	6		0	0
88.8 ± 4.00	2	40	7	91 ± 2.00	0	0
	3	55	8		2	10
	3	70	9		2	20
90.5 ± 5.00	4	90	10	92 ± 3.50	3	35
	2	100	11		3	50
			12		4	70
			13		1	75
			14		3	90
			15		2	100
Latent period[a]		18.2%		Latent period[a]		63.3%

[a]Latent period = no. of 0 day % mortality/total no. of days of 100% death.

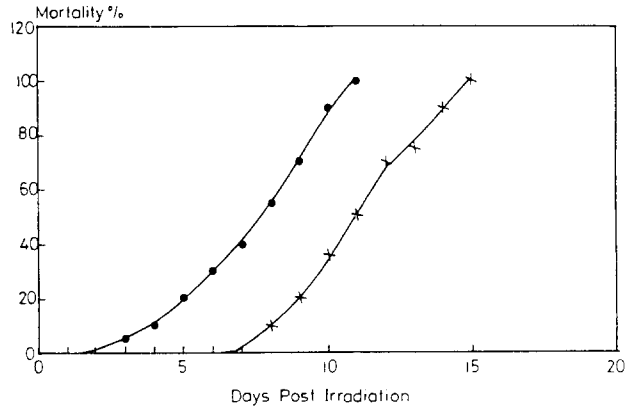

Figure 1. Effect of $SrCl_2$ treatment on mortality % (life span) of γ-irradiated rats (7.5 Gy): (•) Group I (Ir); (×) Group 2 ($SrCl_2$-Ir).

flected at the end of the experimental period (10 days).

The effect of whole body γ-irradiation on serum glucose and liver glycogen levels of exposed rats is presented in Tables 3 & 4. The highly significant increase of serum glucose level in the γ-irradiated rats (Group II) reached its maximum value during the first 24 h up to 72 h post-irradiation (83 and 102%, respectively, $P < 0.01$). The hepatic glycogen content showed a drastic increase in the first 24 h post-irradiation, reaching a value of 203% ($P < 0.01$, Table 4). This period of glycogen increase is followed by a gradual decrease until it reached its minimal value by day 10 (−151.4%, $P < 0.01$).

Our results are in agreement with those of Altman *et al.* (1970) who reported that hyperglycemia developed after exposure of rats to irradiation. In addition, Weber & Cantero (1959) and Sobocinski & Altman (1972) stated that irradiated rats exhibited a transient increase in liver glycogen content on the first and second days post-irradiation, which was then reduced on the third day.

Our findings can be explained on the basis that excessive protein catabolism is one of the most clear post-irradiation features that leads to accumulation of excess amino acids in the liver, and consequently stimulation of gluconeogenesis and glycogenesis pathways. This explanation is supported by the findings of Toropila *et al.* (1986) that the concentration of serum corticosterone was increased in irradiated rats which leads to an increase in the activity of enzymes which regulate the gluconeogenesis process.

In this regard, administration of $SrCl_2$ *per se* showed non-significant changes in the serum glucose level, while the same treatment affected the liver glycogen content, recording a significant decrease of 75.3% at the end of the experimental period ($P < 0.01$, Table 4).

With regard to animals of Group IV ($SrCl_2$-Ir), the drastic hyperglycemic effect of irradiation was somewhat corrected, reaching more or less the

Table 2. Liver wet weight/body weight ratio of rats of all tested groups

Groups	Days post-irradiation			
	1	3	7	10
Group I (NC)	0.040 ± 0.005	0.039 ± 0.005	0.040 ± 0.005	0.040 ± 0.004
Group II (Ir)	0.050 ± 0.002	0.050 ± 0.003	0.047 ± 0.002	0.058 ± 0.003
% change	25	28.2	17.5	45
P value <	0.01	0.01	0.01	0.01
Group III ($SrCl_2$)	0.036 ± 0.004	0.037 ± 0.003	0.044 ± 0.005	0.040 ± 0.007
% change	10	5.1	10	–
P value <	NS	NS	NS	NS
Group IV ($SrCl_2$-Ir)	0.043 ± 0.008	0.041 ± 0.004	0.046 ± 0.003	0.060 ± 0.005
% change	7.5	5.1	15	50
P value <	NS	NS	NS	0.01

Results are means ± SD of six rats. Significant difference from $P < 0.05$.

normal level throughout the experimental period (Table 4). In addition, lesser changes in the hepatic glycogen content on days 1 and 3 post-irradiation were noticed, yet were followed by a significant decrease of 63 and 46.8% on days 7 and 10, respectively ($P < 0.01$, Table 4). This indicated that $SrCl_2$ injection shortly before irradiation promoted glycogenolysis to produce a more or less normal glucose level.

Serum and liver LDH activities in rats subjected to whole body γ-irradiation and/or treated with $SrCl_2$ are given in Tables 3 & 4. These data indicate that γ-irradiation induced a significant increase in the serum LDH activity starting from day 1, shooting up to a maximal increase of 159.4% on day 3 and ending with a less significant increase of 82.3% on day 10 ($P < 0.01$, Table 3). Likewise, liver LDH activity showed a comparatively moderate increase of 31.5 and 24% on days 3 and 10, respectively ($P < 0.01$), reaching a maximal increase of 39% on day 10 ($P < 0.01$, Table 4).

Different assumptions have been suggested to clarify the rise in the activity of this enzyme. Manciulea *et al.* (1978) reported that the change in tissue permeability and the deteriorative effect of γ-irradiation on the different organs could enhance the movement of enzymes from their subcellular site of production to the extracellular spaces and consequently to the blood circulation with a subsequent rise in their concentration. The increase in serum LDH activity can also be explained on the basis of molecular size, as enzymes of a smaller molecular size would leave the cells more rapidly than large ones. LDH has a relatively small molecular weight (134 000) compared with other enzymes and can thus diffuse easily into the blood stream (Albaum 1960).

Administration of $SrCl_2$ *per se* to normal irradiated rats showed non-significant changes in LDH activity in both the serum and liver (Tables 3 & 4).

With regard to administration of $SrCl_2$ before irradiation, the drastic increase in serum and liver LDH, characteristic of γ-irradiation, decreased to only 48.8 and 19%, respectively ($P < 0.05$, Tables 3 & 4). This clearly indicates the effect of $SrCl_2$ administration in affecting the noticeable decrease in this enzyme activity after its drastic elevation due to irradiation.

The effect of whole body γ-irradiation on rats of Group II with respect to serum ALP reveals a significant decrease in its activity which reached 70.5% on day 3 ($P < 0.01$, Table 3). A nearly similar effect was noticed for the liver enzyme activity but differed by day 10, as it increased significantly by 66% ($P < 0.01$, Table 4). Our findings are in accordance with those of Higman & Hanks (1970), who reported that injury of the intestinal mucosa is chiefly responsible for the fall that occurs in the circulating serum ALP activity following irradiation, reaching its minimal level by days 3 and 6, and then returning to normal level by days 7–14.

Stephan *et al.* (1977) attributed this decrease to the degenerative changes and necrosis that appear after irradiation exposure. Recently, Auda *et al.* (1987) reported a decline in liver ALP activity 48 h after whole body X-irradiation of mice.

With regard to group III ($SrCl_2$), serum and liver ALP activities are significantly increased, reaching

Table 3. Serum ALT, AST, ALP and LDH activities and glucose concentration in rats of all groups

	Days post-irradiation															
	Group I				Group II				Group III				Group IV			
Parameter	1	3	7	10	1	3	7	10	1	3	7	10	1	3	7	10
Glucose (mg dl^{-1})																
mean ± SD	78.30 ±13.77	78.30 ±13.7	68.67 ±7	69.90 ±33.76	143.40** ±25.8	158.30** ±16.54	113.50** ±14.45	123.80** ±7.5	79.88 ±12.64	65.89 ±8.18	72.61 ±16.90	67.68 ±23.30	86.63 ±14.00	100.20 ±12.00	88.5*	77.44
% change	—	—	—	—	83.10	102.17	65.30	80.30	1.63	15.8	5.70	1.44	10.60	30.55	28.90	12.77
ALP (k.A.U)																
mean ± SD	30.26 ±3.67	30.26 ±3.67	26.68 ±1.67	28.68 ±1.68	25.69* ±2.10	8.93** ±1.74	12.28* ±1.96	25.35 ±4.10	49.70** ±8.33	56.27** ±10.60	38.50* ±3.74	30.77 ±5.46	34.60 ±3.90	27.55 ±4.40	16.61** ±3.67	28.23 ±2.89
% change	—	—	—	—	−15.10	−70.50	−57.2	−11.60	64.20	86	34.2	7.27	14.5	−8.3	−42	−1.60
ALT (Ul^{-1})																
mean ± SD	58.30 ±3.9	58.30 ±3.9	58.30 ±3.9	58.30 ±3.9	54.60 ±3.70	51.00 ±2.10	75.50** ±5.63	164.60** ±16.8	30.76** ±5.10	43.24* ±14.30	48.07* ±10.60	41.22* ±15.20	30.00** ±5.40	30.90** ±5.10	55.83 ±5.95	103.4** ±12.64
% change	—	—	—	—	−6.3	−12.5	29.5	182.3	−36.9	−25.60	−17.66	−29.30	−48.5	36.6	−4.3	76.6
AST (Ul^{-1})																
mean ± SD	56.30 ±3.04	56.3 ±3.04	56.3 ±3.04	56.3 ±3.04	64.80** ±6.40	48.28** ± 4.00	50.40* ±4.12	72.00** ±5.73	53.15 ±8.40	43.89** ±6.86	50.53 ±9.30	45.96** ±8.16	61.10 ±4.90	54.64 ±3.43	60.40 ±8.57	82.4** ±10.3
% change	—	—	—	—	15.10	−14.2	−13	27.8	−5.6	−22	−10.2	−18.3	8.50	−2.9	7.5	46.3
LDH (Ul^{-1})																
mean ± SD	132.00 ±40	132.00 ±49	112.00 ±44.10	112.00 ±44.10	226.00* ±55.37	344.00** ±62.90	196.23* ±55.00	205.00* ±61.25	156.75 ±49.50	165.30 ±47.40	119.33 ±46.20	148.90 ±17.10	187.00 ±52.90	176.00 ±34.30	82.42 ±21.85	167.00* ±25.4
% change	—	—	—	—	70.40	159.40	74.50	82.30	18.00	24.50	10.00	32.40	41.30	32.67	−26.70	48.8

Number of animals/group = 24. Values are means ± SD of six rats. *$P < 0.05$. **$P < 0.01$.

Table 4. Liver ALT, AST, ALP and LDH activities and glycogen content in rats of all groups

	Days post-irradiation															
	Group I				Group II				Group III				Group IV			
	1	3	7	10	1	3	7	10	1	3	7	10	1	3	7	10
Glycogen (mg g^{-1})																
mean ± SD	0.81	0.81	0.84	0.84	2.45**	1.51**	0.56*	0.37**	0.74	0.64	0.60*	0.21**	0.93	1.00	0.31**	0.45**
	±0.12	±0.12	±0.07	±0.07	±0.39	±0.28	±0.14	±0.05	±0.07	±0.07	±0.19	±0.39	±0.07	±0.24	±0.09	±0.05
% change	—	—	—	—	203	87	−33.50	−56.65	−8	−20.70	−30.76	−75.29	14.70	24.00	−63.00	−46.80
ALP (U g^{-1})																
mean ± SD	5.80	5.80	5.30	5.30	3.93*	1.65**	3.50**	8.82**	6.36	6.33	9.99**	9.36**	7.60	2.60**	6.67	10.70**
	±1.47	±1.47	±10.5	±10.5	±0.97	±0.22	±0.43	±2.2	±0.76	±6.4	±1.47	±1.90	±2.57	±0.36	±1.55	±0.81
% change	—	—	—	—	−32.20	−71.55	−34.6	66.00	9.58	9.1	88.4	74.90	31.00	55.2	25.8	101.00
ALT (U g^{-1})																
mean ± SD	36.00	36.00	36.00	36.00	43.40*	44.60**	43.40**	57.80**	36.36	35.53	24.80**	25.70**	37.20	31.45	9.46	26.6*
	±4.38	±4.38	±4.38	±4.38	±3.80	±2.70	±3.26	±5.67	±4.66	±6.54	±6.62	±5.64	±4.90	±3.75	±5.68	±2.55
% change	—	—	—	—	19.4	24.00	20.5	60.5	0.98	−1.3	−31.1	−28.60	3.30	−13.8	−18.1	−26.00
AST (U g^{-1})																
mean ± SD	16.45	16.45	16.45	16.45	13.66**	14.27*	15.75	27.26**	16.12	18.3	15.31	16.10	17.30	15.93	17.66	16.59
	±1.23	±1.23	±1.23	±1.23	±0.88	±1.59	±1.35	±0.93	±0.61	±1.85	±1.25	±3.00	±1.59	±0.40	±1.15	±2.20
	—	—	—	—	−16.7	−13.25	−4.25	65.70	−2.00	11.24	−6.9	−2.37	5.20	−3.2	7.35	0.9
LDH (U g^{-1})																
mean ± SD	292.00	292.00	292.00	292.00	286.00**	384.00**	405.66**	362.00*	249.00	307.00	341.97	283.95	376.00**	346.00	305.00	347.75*
	±38.90	±38.91	±38.91	±38.91	±40.82	±29.76	±18.30	±42.50	±42.40	±17.91	±34.10	±28.10	±39.10	±53.51	±21.56	±30.50
	—	—	—	—	−32.20	31.50	39.00	24.00	−14.60	5.10	17.10	−3.00	25.70	18.50	4.40	19.10

Number of animals/group = 24. Values are means ± SD of six rats. * $P < 0.05$. ** $P < 0.01$.

their maximal values on days 3 and 7 post-irradiation (86% and 88.4%, respectively $P < 0.01$, Tables 3 & 4).

Serum ALP activity returned to its normal level on day 10 while its activity in the liver remained elevated up to day 10, recording a significant increase of 74.8% ($P < 0.01$, Table 4).

Rats that received $SrCl_2$ shortly before irradiation (Group IV) exhibited a more or less neutralizing pattern on the serum ALP, as it reached its normal level by the end of the experimental period. In contrast, liver ALP activity showed a sharp increase of 101% by day 10 ($P < 0.01$, Table 4). This indicates that it is mostly affected with the irradiation where hazards usually stay longer and appear profoundly later in time.

Serum and liver ALT activities showed increases of 182.3 and 60.5%, respectively, on day 10 post-irradiation ($P < 0.01$, Tables 3 & 4), while serum and liver AST activity exhibited a more or less milder increase in the irradiated non-treated group (27.8 and 65.7%, respectively, $P < 0.01$, Tables 3 & 4).

It seems possible to expect that whole body exposure to ionizing radiation induced effective changes in the activity of these enzymes and thus unexpected alterations in their activities. The lower levels of serum ALT and AST activities recorded in the early stages after irradiation could be attributed to either excessive excretion through the kidneys and bile or inactivation in their biosynthesis (Wilkinson 1962, Manciulea 1978). Jungowska *et al.* (1975) reported that a marked increase occurs in ALT and AST activities in liver, kidney and spleen homogenates of mice after whole body exposures to 9 Gy, which is attributed to the effect of ionizing radiation on the permeability of the mitochondrial membrane. Manciulea *et al.* (1978) noticed a clear increase in rat liver and plasma ALT activity on day 9 post-irradiation, while serum AST activity was decreased 2 days post-irradiation. Toropila *et al.* (1986) reported a similar increase in liver ALT after whole body exposure to X-rays, which is in line with our findings.

Administration of $SrCl_2$ alone is found to exert different changes on the activity pattern of both enzymes in the serum and liver tissue which are milder than those occuring due to the irradiation effect only.

With regard to Group IV ($SrCl_2$-Ir), the activity of serum ALT, which is a more specific prognostic parameter for liver condition, showed a marked increase of 76.6% by day 10, compared with irradiated untreated rats (Table 3). In this regard, liver ALT activity is affected by this mode of treatment as it showed only a mild decrease of 26% by the end of the experiment, as compared with a marked increase of 60.5% recorded for irradiated untreated rats ($P < 0.01$, Table 4).

The effect of $SrCl_2$ injection prior to irradiation on serum AST activity is clear as it showed non-significant changes up to day 10 on which an increase of 46.3% was recorded ($P < 0.01$, Table 3). Also, a promising effect is reported on liver AST activity in rats of group IV.

In the present study, $SrCl_2$ exerted a beneficial effect as a radioprotector substance, since the above mentioned subclinical symptoms were ameliorated to a certain extent by the administration of $SrCl_2$ prior to whole body γ-irradiation.

The beneficial effect of $SrCl_2$, may be explained as follows:

$$\text{I} \quad SrCl_2 \leftrightharpoons Sr^{++} + 2Cl^-$$
$$\text{II} \quad Sr^{++} + 2OH^- \leftrightharpoons Sr(OH)_2$$
$$\text{III} \quad H^+ + HCO_3^- \leftrightharpoons H_2CO_3$$
$$\text{IV} \quad Cl^- + NH_4^+ \leftrightharpoons NH_4Cl$$

and with an oscillating electron (s) between the produced $H^{\cdot}$ and $OH^{\cdot}$ (by irradiation) and due to elimination of the hydroxyl groups (equation II), thus these radicals can be excreted as ions; also, due to the blood buffering system and renal regulation of acid–base balance, H^+ and Cl^- ions can be differentially excreted (equations III and IV).

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