

Table 1. *Organs of hematopoiesis and immunopoiesis*

Hematopoiesis organ	General characteristics, functions	Location. General notion for human	Features of laboratory animals in comparison with human	Source
Red bone marrow (RBM)	Central organ of hematopoiesis, immunopoiesis and meelopoiesis, formation of T-lymphocytes, antigen independent differentiation of B-lymphocytes	Located in epiphysis of tubular bones, spongy substance of flat bones, in shoulder blades and sternum, vertebrae, cranium bones. In the newly-born RBM takes all bone marrow cavities. A child in the age from 10 to 12 years old has only RBM. Until the age from 20 to 25 years old yellow bone marrow completely fills bone marrow cavities of long tubular bone diaphysis. Until 30 years old correlation of fatty and blood forming red marrow equals to correlation of 50%. Until 70 years old correlation includes 70%–30%	Mice, rabbits and mini pigs: different from human it contains less quantity of blood forming cells and has higher contents of fatty cells. Dogs, cats: more blood forming cells than fatty cells.	[9]
Thymus (thymus gland)	Central organ of lymphocytopoiesis and immunogenesis. In thymus such hormones as thymosin, thymulyn, thymopoetin and insulin similar factor of growth 1	Located in the upper part of rib cage, consists of two parts. In human organism maximal development is typical for early age from 3 to 18 years old which is weight stabilization. After 20 years old age thymus evolution takes place. Until the age of 50 or 60 years weight of thymus decreases approximately in two or three times and is accompanied by morphological changes such as increasing of part of fatty and combining tissue, reducing of epithelial parenchyma and lymphoid component	<u>Mice</u> : presence of two thymuses both in the rib cage and in cervical spine, involution is after two months old. <u>White rats</u> : thymus growth is until five months old; age involution is after six months old and from the 2nd year, it is speeded involution. <u>Rabbits</u> : thymus growth is until six months old, after three years old thymus involution start, high addiction of immune system organs morphology to existence condition. Early involution starts due to little movement of animals, hunger and hypoxia. <u>Cats, dogs</u> : thymus of not big sizes, involution starts after five or six months old, reduces until two or three years old. <u>Pigs</u> : thymus is strongly developed, reduces until two or three years old	[12–15]
Spleen	Peripheral immune system organ. Functions: 1. Antigen addicted lymphocytes differentiation. 2. Production of antibodies, depressant substances for erythropoiesis in red bone marrow. 3. Elimination from blood flow and destroying of old and damaged erythrocytes and thrombocytes. 4. Blood depositing and thrombocytes accumulation	Spleen is located in the left iliac region approximately parallel to curve line of stomach in human organism, under ribs on the left side. In spleen white and red pulps are differentiated. Red pulp includes about 75% of amount and consists of reticular tissue with cell blood elements and blood vessels. Characteristics of parameters of red and white pulp depend on migration properties of immunocompetent cells, degree of immune processes activity. The spleen in adults does not participate in hematopoiesis	Morph-functional types of mammal spleen on the base of histeometric capsule indexes, white pulp: 1. Protecting type of rabbits, gophers and marmots. 2. Depositing type of horses and pigs. 3. Mixed type (depositing and protecting type) of dogs, cats, goats, foxes, ferret. True differences in red pulp of spleen in different groups of mammals have not been found out. The spleen plays an important role in hematopoiesis in adult animals, and in rodents throughout their lives	[9, 16–19]
Lymph nodes	Peripheral organ of lymphopoiesis. The main function is protection. In lymph nodes proliferation or cloning and differentiation of T- and lymphocytes to effector cells takes place and formation of T and W- cells of memory takes place	Lymph nodes are formations of circle shape, oval shape, bean shape, rarer tape form are in size from 0,5 to 50 mm locate in groups on the ways of lymph vessels from organs and tissues to lymph flows and lymphatic trunks	In animals' organisms a few types of lymph nodes are differentiated: 1. Concentrated type of rabbits: few big lymph nodes. 2. Dispersive type of horses: big quantity of tinny lymph nodes located as packages. 3. Mixed type of pigs.	[20]

Table 1 (continued)

Hematopoiesis organ	General characteristics, functions	Location. General notion for human	Features of laboratory animals in comparison with human	Source
Palatine tonsils	Basic functions include: 1. Providing organism with immunocompetent cells through lymphatic system. 2. Protection of upper respiratory tract from infections. 3. Forming bacterial flora for mouth cavity and nasopharynx. In tonsils secretory IgA, interferon and in less amount IgM, IgG actively synthesize	Tonsils represent accumulation of lymphoid tissue located on both side of entrance to pharynx. Between tonsils and thymus, there is a functional connection. Tonsils Removing causes early thymus involution.	Types of tonsils: 1. ruminants, single-hoofed animals, carnivore animals, humans have paired tonsils but most of omnivores don't have them; 2. single-hoofed animals and omnivores have one non-paired soft pallet tonsil; 3. omnivores and tinny ruminants have a near epiglottis tonsil; 4. all kinds of mammals have three-tongued and pharynx	[15, 21, 22]
Peyer's patches of the intestine	Participate in immune response forming including development of allergy on food allergens, in maturation of T- and W lymphocytes. Functions are explored not completely.	Lymphoid tissue of small intestine as nodule accumulations is associated with mucous covers, it contacts with contents of gastrointestinal tract, microflora, parasites, toxins, etc.	Peyer's patches of different mammal kinds have similar structure but can vary by size, quantity of follicles and cell compound.	[23, 24]

The table is prepared by the authors

Table 2. Examples of drugs exhibiting hematotoxicity

Mechanism of toxic action development	Drug	Effect	Source
Cytotoxic effect on hematopoietic predecessors cells	Linezolid (antibiotic)	Inhibition of mitochondrial protein synthesis => development of myelosuppression	[25]
	Chloramphenicol (antibiotic)	Development of myelosuppression or aplastic anemia (mechanism unknown)	[25]
	H2-histamine receptor blockers (cimetidine, famotidine, ranitidine)	Direct defeat of myelopoiesis predecessors	[27]
	Lindane (antiparasitic medicine)	Cytotoxic effect on hematopoietic predecessors' cells => necrosis => myelosuppression	[29]
	Interferon alfa	Suppressive effect on pluripotent progenitor cells => leucopenia, thrombocytopenia	[31]
Direct damage to mature cells by toxicants	Clozapine (antipsychotic drug)	Glutathione-induced apoptosis and secondary oxidative stress due to depletion of adenosine triphosphate stores => neutrophil apoptosis	[27]
Indirect damage of blood cells or bone marrow	Cephalosporins (ceftriaxone, ceftazidime), Penicillins (piperacillin), probenecid, Nonsteroidal anti-inflammatory drugs (ibuprofen), sulfonamides, quinine	The drug or its metabolite binds to some of the proteins of the erythrocyte membrane, antibodies are formed (IgM and IgG types against the complex), which activates the complement system and leads to intravascular hemolysis and the development of anemia	[25, 30]
	Methyldopa (antihypertensive medicine)	Change in the structure of red blood cell membranes => the body perceives them as foreign => the appearance of antibodies to red blood cells	[25, 30]
	Paclitaxel (anti-cancer drug)	The bone marrow microenvironment changes => the sensitivity of late erythroid precursors to erythropoietin decreases => depletion of erythroid precursors during late erythropoiesis	[29]
	Ribavirin (antiviral medicine)	Passive hemolysis with heme release => anemia	[28, 31]
Effect on enzyme systems	Aspirin, various non-selective NSAIDs that inhibit cyclooxygenase-1 activity Gold-containing drugs	Irreversible inhibition of cyclooxygenase-1 => thromboxane A2 synthesis is blocked and platelet aggregation is suppressed.	[25]

The table is compiled by the authors

Оценка функциональной безопасности органов кроветворения в исследованиях токсикологических свойств лекарственных препаратов: обзор. Часть 1. Органы кроветворения лабораторных животных. Механизмы развития гематотоксичности

Таблица 3. Референтные значения показателей общего анализа крови лабораторных животных (грызунов)
Table 3. Data on the reference values of the total blood count of laboratory animals (rodents)

Показатель <i>Indicator</i>	Мышь <i>Mouse</i>		Крыса <i>Rat</i>		Хомяк <i>Hamster</i>		Морская свинка <i>Guinea pig</i>	
	Самец <i>Male</i>	Самка <i>Female</i>	Самец <i>Male</i>	Самка <i>Female</i>	Самец <i>Male</i>	Самка <i>Female</i>	Самец <i>Male</i>	Самка <i>Female</i>
Эритроциты, RBC ($\times 10^{12}/л$)	6,9–12 [33] 7,3–10,8 [34] 5,6–8,5 [35]	6,9–11 [33] 6,4–10,8 [34] 4,3–9,8 [35]	8,2–9,8 [33] 6,2–9,1 [34]	6,8–9,2 [33] 6,0–9,0 [34]	4,7–10 [33] 7,8–9,3 [37]	3,9–9,9 [33] 7,5–9,9 [37]	4,8–6,2 [38] 5,5–6,1 [39] 4,4–6,8 [40]	4,4–6,1 [38] 5,3–5,7 [39] 3,4–6,2 [40]
Гематокрит, HCT (%)	33–50 [33] 42–62 [34] 32–50 [35]	40–45 [33] 40–57 [34] 29–55 [35]	44–50 [33] 39–52 [34]	38–51 [33] 36–50 [34]	47–57 [33]	39–59 [33]	41–52 [38] 45–51 [39] 37–47 [40]	40–51 [38] 45–50 [39] 41–50 [40]
Гемоглобин (г/дл)	11–12 [33] 4,5–18,5 [34] 10–17 [35]	10–11 [33] 12–18,2 [34] 9,5–19 [35]	13–16 [33] 13–18 [34]	12–16 [33] 13–18 [34]	14–19 [33] 12–15 [37]	13–19 [33] 12–16 [37]	13–17 [38] 14–15 [39] 12–17 [40]	13–17 [38] 14–15 [39] 11–17 [40]
Средний объем эритроцита, MCV (фл)	48–51 [33] 36–64 [34]	47–52 [33] 49–65 [34]	50–58 [33] 49–70 [34]	51–66 [33] 52–65 [34]	64–78 [33] 49–52 [37]	64–76 [33] 49–54 [37]	78–88 [38] 82–85 [39] 71–83 [40]	79–95 [38] 84–86 [39] 86–96 [40]
Среднее содержание гемоглобина в эритроците, MCH (пг на клетку)	12–13 [33] 14–20 [34]	11–13 [33] 15–23 [34]	14–18 [33] 17–24 [34]	16–19 [34] 18–25 [35]	20–25 [33] 16–17 [37]	20–26 [33] 15–17 [37]	25–27 [38] 24–27 [39]	25–28 [38] 23–26 [39]
Средняя концентрация гемоглобина в эритроците, MCHC (г/дл)	23–31 [33] 26–36 [34]	22–30 [33] 25–36 [34]	26–35 [33] 30–40 [34]	27–36 [33] 30–41 [34]	28–37 [33] 30–32 [37]	28–37 [33] 30–32 [37]	32–34 [38] 29–32 [39] 30–39 [40]	30–34 [38] 28–34 [39]
Ретикулоциты (%)	1,8–3,3 [34]	0,7–4,3 [34]	1,2–3,5 [34]	1,3–2,8 [34]	0,20–3,0 [36]	0,60–3,6 [36]	0,7–3,1 [36] 0,6–1,4 [39]	0,4–2,8 [36] 0,4–1,4 [39]
Тромбоциты ($\times 10^9/л$)	157–412 [33] 855–1770 [34] 60–522 [35]	170–410 [33] 612–1509 [34] 37–650 [35]	789–1363 [34]	737–1460 [34]	367–573 [33] 328–594 [37]	300–490 [33] 213–578 [37]	197–636 [38] 375–470 [39] 260–740 [40]	335–1000 [38] 389–495 [39] 266–634 [40]
Лейкоциты WBC ($\times 10^9/л$)	13–16 [33] 2,9–16,2 [34]	12–14 [33] 2,1–8,3 [34]	8,0–12 [33] 5,2–19 [34]	6,6–13 [33] 3,9–21 [34]	5,0–10 [33] 1,5–5,9 [37]	6,5–11 [33] 0,9–11 [37]	5,5–18 [38] 3–11 [39] 4,7–7,1 [40]	5,2–16 [38] 2,1–9,0 [39] 4,1–6,9 [40]
Нейтрофилы (%)	13–22 [33]	16–19 [33]	6,2–43 [33]	4,4–49 [33]	17–27 [33]	23–35 [33]	29–40 [39] 28–56 [40]	26–39 [39] 20–42 [40]
Лимфоциты (%)	62–83 [33] 59–96 [34]	66–78 [33] 63–95 [34]	58–83 [33] 67–97 [34]	50–85 [33] 69–98 [34]	55–92 [33]	51–85 [333]	18–59 [38] 49–64 [39] 40–63 [40]	18–73 [38] 52–67 [39] 46–80 [40]
Эозинофилы (%)	1,4–2,8 [33] 0,00–7,0 [34]	2,1–2,8 [33] 0,00–7,0 [34]	0,10–0,63 [33] 0,0–3,0 [34]	0,0–1,9 [33] 0,0–2,0 [34]	0,26–1,5 [32]	0,2–1,2 [33]	0,00–6,0 [38] 3,5–6,7 [39] 1,0–7,0 [40]	0,00–9,0 [38] 3,0–6,5 [39] 0,00–7,0 [40]

Продолжение таблицы 3
Table 3 (continued)

Показатель Indicator	Мышь Mouse		Крыса Rat		Хомяк Hamster		Морская свинка Guinea pig	
	Самец Male	Самка Female	Самец Male	Самка Female	Самец Male	Самка Female	Самец Male	Самка Female
Базофилы (%)	0,22–0,82 [33] 0,0–1,0 [34]	0,13–0,85 [33] 0,0–1,0 [34]	0,00–0,60 [33] 0,0–1,0 [34]	0,00–0,40 [33] 0,0–1,0 [34]	0,00–5,0 [33]	0,00–2,1 [33]	0,0–2,0 [38] 0,0–1,1 [39] 0,0–1,7 [40]	0,0–2,0 [38] 0,0–1,6 [39] 0,0–0,80 [40]
Моноциты (%)	2,2–2,5 [33] 0,0–8,0 [34]	0,98–1,1 [33] 0,0–9,0 [34]	0,0–0,65 [33] 1,0–9,0 [34]	0,0–1,8 [33] 0,0–9,0 [34]	0,9–4,1 [333]	0,4–4,4 [33]	0,0–10 [38] 1,0–4,0 [39] 3,3–5,3 [40]	1–7 [38] 1,5–4,1 [39] 1,0–2,6 [40]

Таблица составлена авторами / The table is prepared by the authors
Примечание. Количество животных (n) [33], [40] — не указано; [34] n=53–61; [35] n=22; [37] самцов n=6; самок n=12; [38] самцов n=93; самок n=37; [39] самцов n=83, самок n=53.

Таблица 4. Референтные значения показателей общего анализа крови лабораторных животных (негрызунов)

Table 4. Data on the reference values of the total blood count of laboratory animals (non-rodents)

Показатель Indicator	Кролик Rabbit		Карликовая свинья Mini Pig		Хорек Ferret		Макаки Macaque	
	Самец Male	Самка Female	Самец Male	Самка Female	Самец Male	Самка Female	Самец Male	Самка Female
Эритроциты ($\times 10^{12}/л$)	5,8–6,8 [41] ^а 4,4–9,4 [42] 4–7 ¹ _б		7,6±0,8 [45] 5,1–9,5 [46]	8,1±0,8 [45] 3–9,4 [46]	7,4–13 [41] 7,1–10 [48]		5,1–6,8 [49] 5,6±0,5 [50] 6,3±0,6 [51]	4,9–6,5 [49] 5,0±0,2 [50] 6,2±0,5 [51]
Гематокрит HCT (%)	28–48 [42] 41,7–57 [44]	33,1–47,7 [44]	46±5,6 [45] 23–57 [46]	50±4,5 [45] 22–56 [46]	47–59 [41] 37–55 [48]		35–54 [49] 41±1,7 [50] 39 ± 2,7 [51]	39–51 [49] 36±2,4 [50] 37±4,0 [51]
Гемоглобин (г/дл) Hgb (g/dL)	9,0–15,4 [42] 10–15 14,7–20,8 [44]	10,8–17,5 [44]	15±1,8 [45] 8,1–19 [46]	17±1,5 [45] 7,0–19 [46]	14,5–18,5 [41] 12–16 [48]		11–17 [49] 14±0,50 [50] 14±0,91 [51]	12–15 [49] 12±0,90 [50] 13±1,32 [51]
Средний объем эритроцита, MCV (фл)	60–75		60±2,6 [45] 46–65 [46]	61±1,8 [45] 48–69 [46]	50–61 [41] 46–55 [48]		68–90 [49] 74±3,7 [50] 63±6,5 [51]	72–87 [49] 72±3,6 [50] 60±3,9 [51]
Среднее содержание гемоглобина в эритроците, MCH (пг на клетку)	19–23 20–26 [44]	19–25 [44]	20±0,9 [45] 14–22 [46] 17–26 [47]	20±0,8 [45] 14–22 [46] 17–28 [47]	14–18 [48]		20–26 [49] 24±1,7 [50] 21 ± 2,1 [50]	22–27 [49] 24±1,1 [50] 20±1,5 [51]

¹ Varga M. Textbook of rabbit medicine. London: Butterworth–Heinemann; 2013 (здесь и далее в таблице для значений без указания литературной ссылки).

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Продолжение таблицы 4
Table 4 (continued)

Показатель <i>Indicator</i>	Кролик <i>Rabbit</i>		Карликовая свинья <i>Mini Pig</i>		Хорек <i>Ferret</i>		Макаки <i>Macaque</i>	
	Самец <i>Male</i>	Самка <i>Female</i>	Самец <i>Male</i>	Самка <i>Female</i>	Самец <i>Male</i>	Самка <i>Female</i>	Самец <i>Male</i>	Самка <i>Female</i>
Средняя концентрация гемоглобина в эритроците, МСНС (г/дл)	34,5		33±0,5 [45] 28–35 [46] 32–36 [47]	34±0,5 [45] 29–37 [46] 32–38 [47]	Данные не представлены		27–34 [49] 33±0,60 [50] 34±0,50 [51]	28–33 [49] 33±0,60 [50] 34±0,55 [51]
	1,9–3,8 [41]		0,20–25 [46]	0,20–23 [46]	≤12 [41]		26–210 [49] 63±18 [50]	40–131 [49] 79±32 [50]
Ретикулоциты (%)								
Тромбоциты	225–905 [42] 250–600		415±158 [45] 87–700 [46] 93–507 [47]	324±82 [45] 129–786 [46] 56–340 [47]	172–1281 [41]		275–742 [49] 346±103 [50] 410 ±104 [52]	332–673 [49] 313±90 [50] 437±78 [52]
	135–1005 [44] 62–1188 [44]				277–732 [48] 278–882 [48]			
Лейкоциты WBC (×10 ⁹ /л)	2,7–12,2 [42] 5–12		10±1,8 [45] 5,9–35 [46]	11±1,9 [45] 6,7–28 [46]	1,7–13,4 [41]		4,5–22 [49] 14±4,8 [50] 9,8±2,7 [51]	5,6–27 [49] 13±3,8 [50] 8,0±1,9 [51]
	2,9–8,9 [44] 1,4–8,2 [44]							
Нейтрофилы (%)	30–50		38±12 [45] 11–64 [46]	25±8,1 [45] 9,4–62 [46]	22–75 [41]		8,3–89 [49] 57±19 [52] 45±13 [53]	25–87 [49] 54±14 [52] 47±16 [53]
	27–73 [44] 24–79 [44]							
Лимфоциты (%)	30–60		51±13 [45] 24–83 [46] ≤90 [47]	63±8,2 [45] 29–82 [46] ≤99 [47]	20–73 [41]		9,8–87 [49] 36±18 [52] 47±12 [53]	11–71 [49] 39±13 [52] 44±14 [53]
					40–82 [48] 40–86 [48]			
Эозинофилы (%)	0–5		2,9±1,1 [45] 0,40–6,4 [46] ≤7,3 [47]	3,2±1,8 [45] 0,30–6,6 [46] ≤9 [47]	0,0–5,7 [41]		0,10–3,4 [49] 3,4±1,5 [52] 0,8±1,2 [53]	0,10–2,7 [49] 3,6±1,1 [52] 0,8±0,9 [53]
					1,9–8,0 [48] 2,2–6,2 [48]			
Базофилы (%)	0–8		0,8±0,21 [45] 0,4–2,1 [46] ≤2,8 [47]	1,2±0,33 [45] 0,40–1,9 [46]	0,0–1,4 [41]		0,10–0,80 [49] 0,14±0,14 [52] 0,15±0,10 [53]	0,10–0,90 [49] 0,10±0,10 [52] 0,19±0,12 [53]
					0,3–1,5 [48]			
Моноциты (%)	2–10		5,4±1,3 [45] 1,9–7,8 [46] ≤9,7 [47]	5,5±1,0 [45] 2,7–11 [46] ≤8,0 [47]	0,0–6,5 [41]		0,50–5,9 [49] 6,2±2,2 [52] 2,5±1,2 [53]	1,1–4,9 [49] 6,6±3,4 [52] 2,5±1,0 [53]
					6,5–9,4 [48] 4,1–11 [48]			

Таблица составлена авторами / The table is prepared by the authors
Примечание. Количество животных (n) – [41] n=105–106; [42] n=937–1559; [43, 45, 47, 52] – не указано; [44] самцы n=24, самки n=16; [46] самцы n=58, самки n=66; [48] самцы n=47, самки n=38; [49] самцы n=76, самки n=37; [50] самцы n=6, самки n=5; [51] самцы n=21, самки n=13; [52] самцов n=28; самок n=14; [53] самцов n=35, самок n=37.