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Review

VANADIUM IN THE ENVIRONMENT AS A RISK FACTOR CAUSING NEGATIVE MODIFICATION OF CELL DEATH (SCIENTIFIC REVIEW)

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The review dwells on results obtained via examinations that focused on effects produced by vanadium and its compounds contaminating the environment on health disorders related to cell death deregulation.

Research works that have been performed over the last decades and focused on revealing the essence of apoptosis mechanism under exposure to technogenic chemicals are truly vital due to this phenomenon having great biological significance within a system of a body trying to adapt to influences exerted by environmental factors.

The present work focuses on apoptosis peculiarities under exposure to excess technogenic concentrations of vanadium compounds. Published research works have been analyzed, analysis results are outlined, and a scientific hypothesis has been formulated within the subject matter. We have described an immune-modulating effect produced by vanadium compounds that is able to modify apoptosis events due to changes in cell death modes (apoptosis activation/inhibition) and it provides body adaptation to changing environmental conditions.

A range in vanadium concentrations between essential and toxic ones predetermines multi-directional changes in apoptosis induction and completion. Thus, induced apoptosis activation makes for development of autoimmune and immune-proliferative processes; at the same time, cell death inhibition can result in immune deficiency, inflammatory reactions, and neurodegenerative diseases. It was shown that vanadium compounds produced modifying effects on mitochondrial functions regulation, changes in phosphorilation/dephosphorilation ratio in protein products, and imbalance in free radical processes; all this ultimately disrupts a balance between pro- and anti-apoptotic signals in a cell. Monitoring over apoptosis parameters that characterize cell death under exposure to vanadium and its compounds will allow timely detecting risks of pre-nosology state occurrence and prevent damage to health.

Key words: *risk, vanadium, environment, cell death, apoptosis mechanism, mitochondrial activity modification, free radical oxidation, damage to health.*

A risk that damage to health will occur under exposure to technogenic chemicals in the environment is realized with the immune system directly participating in the processes at early stages in a disease. The immune system is a most significant regulatory one that provides adequate adaptation of a body to impacts exerted by environmental factors including various chemicals. Cell death plays a key role in immune regulation. Cell death is a process that involves irreversible changes in vital cellular functions (primarily, adenosine

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triphosphate synthesis and redox homeostasis preservation); it results in cell integrity loss (disorders in plasmatic membrane permeability or cell fragmentation) [1]. Cell death can be regulated and genetically programmed (regulated cell death, RCD) or accidental (accidental cell death, ACD). Regulated cell death occurs due to activation of one or several signal cascades and is modulated (regulated) via pharmacological or genetic interferences. RCD includes apoptosis, autophagy, anoikis, pyroptosis, partanosis, and necroptosis [2].

Apoptosis is an evolutionary conservative process which is necessary for maintaining cellular homeostasis in a body. Apoptosis regulates balance between proliferation, differentiation, and elimination of cells that are no longer necessary. Accidental cell death (ACD) is instant and uncontrollable cell death when plasmatic membrane is destroyed completely due to extreme physical, chemical, or mechanic factors. Necrosis is traditionally seen as an accidental and non-regulated cell event.

Chemicals with different essence cause persistent hazards for human health in contemporary social, economic, and ecological conditions. Vanadium is among most significant environmental contaminants; being a hapten, it exerts adverse impacts on the cardiovascular, respiratory, and reproductive systems and produces neurotoxic and immune-toxic effects [3]. But at the same time, the latest achievements in medicine such as creation of vanadium-containing orthodontic / orthopedic implants and development of anti-parasitic, antiviral, anti-bacterial, anti-thrombotic, anti-hypertensive, hypolipidemic, spermicidal, anti-tuberculosis, anti-tumor, and anti-diabetic medications make it necessary to resolve disputable issues related to influence exerted by vanadium on the immune system [4–9]. Adverse consequences caused by effects produced by chemical environmental factors on human health can become apparent not only via immune-dependent diseases occurrence but also failure in body adaptation mechanisms. Disorders in regulated cell death are a reason for deadaptation that occurs under exposure to chemicals. It has been established that different metals and organic compounds can modify cell death mechanisms [10–12]. But at the same time as we generalized and analyzed literature data, we revealed certain contradictions regarding influence exerted by different chemical factors on cell death.

Despite there are multiple published works that focus on how lethal programs in cells are realized, there is no scientifically substantiated concept about modifying effects produced by vanadium on apoptosis. The present work concentrates on peculiarities of apoptosis under exposure to vanadium.

Vanadium (hapten) is a biologically significant element that participates in many physiological processes [13–16]. Vanadium is n ultra-microelement and it occurs in trace quantities in all organs and tissues in a human body [9, 17]. Overall, according to generalized data, vanadium contents in a body amount to lower than 10 ng/g of body weight [7]. Vanadium is detected in the heart, kidneys, liver, brain, muscles, bones, fat tissue, testicles, thyroid gland, colostrums, breast milk, and hair [3, 7, 9, 18, 19].

Vanadium enters a body from the environment predominantly via the gastrointestinal tract or bronchopulmonary system. In occupational environment vanadium and its compounds can also enter a body via skin and eye mucosa [20]. It has been shown that vanadium that enters a human body with food is poorly absorbed in the gastrointestinal tract (from 0.2 to 1.0 %). Most vanadium that was consumed orally turns into poorly soluble vanadium dioxide (IV) $VO(OH)_2$ and is extracted with feces; due to it, it doesn't cause any potential hazard for human health [21]. However, a decrease in overall fat, carbohydrates, and proteins consumption can influence vanadium absorption [7].

Primarily vanadium enters a body via respiratory tracts. Respiratory organs are basic target ones when it comes to inhalation

exposure to vanadium. It was shown that already after a 2-day chronic exposure to vanadium in doses equal to 0.28 mg/m^3 mice and rats had changes in their lung tissue that involved inflammation, fibrosis, and cell hyperplasia in bronchiolar and alveolar epithelium [22]. Health disorders among children and adults occur due to impacts exerted on them by high vanadium concentrations in ambient air as well as in working area air [4, 8]. Size of vanadium-containing particles and vanadium compounds solubility are significant factors determining a rate at which vanadium is absorbed in respiratory tracts.

Previous research revealed that vanadium that entered a human body caused changes in immune reactivity and increased genetic variability in population. Workers employed at a metallurgic enterprise where a full cycle for vanadium iron production was used had by up to 37 % greater quantity of apoptotic cells and lymphocytes expressing CD25$^+$-receptor in their bodies in case vanadium was identified in their blood at a level close to an upper boundary of a reference value [13]. Pro-apoptotic cytokines hyper-production and hyper-expression of early activation CD25 marker as well as growth in Annexin V-positive lymphocytes quantity were detected in examined children who lived under chronic aerogenic exposure to V_2O_5 that was introduced into ambient air as a component in industrial emissions from metallurgic productions. Studies on gene polymorphism under exposure to vanadium allowed revealed polymorphic changes as per heterozygote type in genes of P450 (*CYP2D6rs38*) cytochrome, corpoporhyrine genase (*CPOXrs1131857*), methylentetrahydrofolate reductase (*MTHFRrs1801133*), and peroxisome proliferation (*PPARG rs4253778*) that were responsible for the 1st and 2nd stage in metals detoxification. For example, frequency of mutant gene *CYP2D6rs38* was 4.3 times higher among adults who were exposed to vanadium than among non-exposed ones. Children exposed to vanadium had polymorphic changes that involved heterozygote polymorphism of genes responsible for detoxification and oxygenation (*CPOX*, sulf transminase – *SULT1rs9282861*, glutathione transferase – *GSTA4rs3756980*). It was established that children exposed to vanadium had mutant allele 4 times more frequently than non-exposed ones.

Vanadium is to a greater extent absorbed in a body as vanadate anion than as vanadyl-cation. In certain physiological states vanadium occurs in a body as vanadates (oxidation rate^{5+}), meta-vanadate (VO^{3-}), and probably ortovanadate (VO_4^{3-}). Vanadium is able to change its oxidation rate when it travels from one medium to another and it results in vanadyl spontaneously transferring into vanadate and back again. A rate at which vanadium compounds transform in a body and types into which they transform have considerable influence on a share of absorbed vanadium. Vanadium has another significant property and it is its ability to create new types; this ability depends on biologic or synthetic chelators or biogenic ligands being present in a body [23].

When vanadium enters the systemic blood flow, it gets bonded to plasma proteins, in particular, to transferrin and albumin and low-molecular ligands such as citrate, oxalate, lactate, phosphate, glycine, hystidine, as well as with hemoglobin; if a concentration is high, it can also create a bond with immunoglobulin G [6, 8, 24, 25]. Vanadium contents in blood fall by approximately 30 % during the first 24 hours after it has entered a body [26]. But at the same time vanadates are able to replace phosphates in bone tissue and it leads to vanadium accumulation and long-term persistence in bones, longer than 1 month [27].

Vanadium penetrates into a cell due to transport structures in cell membranes (transporters, phosphates or sulfate-ion channels) or receptor-mediated endocytosis [3]. As vanadium has a strong ability to change oxidation or exchange ligands (H_2O, CO, H^+, OH^-, Cl^-, PO_4^{3-} etc.) depending on the micro-environment, molecules that are close to it can exert significant influence on vanadium transporta-

tion through cell membranes. Vanadium distribution inside cells depends on what vanadium compound has penetrated a body. In a cell vanadium interacts with glutathione, ascorbic acid, or nicotinamide adenine dinucleotide (NADH) and it results in its recovery from V^{5+} to V^{4+} [8, 9, 28]. And here vanadyl (four-valent state) prevails inside a cell. Intracellular oxidizers such as NAD^+, O_2 и O_2^{2-} can oxidize vanadyl back into vanadate [3]. Mutual transformation between different vanadium types in a cell (basically V^{+4}/V^{+5} and to a lesser extent V^{+3}) occurs constantly. Different compartments in a cell have different pH and due to it they have different ability to absorb and accumulate vanadium [7]. Inside a cell vanadium compounds can either exert direct influence on various organelles thus changing their functional activity or they can interact with a wide range of protein molecules and modify intracellular signal cascades.

Mice that had been aerogenically exposed to vanadium (V) had inflammatory processes in their lungs 6 hours after the exposure; after 72 hours there was a significant increase in apoptotic cells quantity. Absorbed vanadium stimulated NADH-oxidase activity of mitochondria responsible for apoptosis realization [28]. Experimental models *in vitro* and *in vivo* allowed establishing dose-dependent effects produced by sodium ortovanadate (Na_3VO_4) on anaplastic carcinoma in the thyroid gland; the effect involved the cellular cycle stop at G2/M phase and a decrease in mitochondria membrane potential (Ψ) [29]. It was proven that decavanadate changed antioxidant enzymes activity when accumulating in mitochondria and also induced mitochondrial membranes de-polarization [30]. Human cholangiocarcinoma (PC-1) cells were used in an experiment and it allowed establishing that V^{5+} inhibited an electrons transfer chain and apoptosis induction an also led to mitochondrial potential collapse (ΔΨ) [4]. Isolated mitochondria from rat liver were treated with five-valent vanadium (concentrations ranging from 25 to 200 μM) and it resulted in cytochrome *c* release from mitochondria [31]. Mitochondria membrane potential went down by 50 % when human hepatocellular carcinoma (HepG2) cells were incubated for 72 hours with VO (250 μg/mL) [32]. Besides, vanadium can have direct influence on internal mitochondria membrane and it can later disrupt electrons transfer between respiratory complexes thus resulting in excessive reactive oxygen species (ROS) occurrence in mitochondria [33]. Considerable ROS production also results from p53 activation. We should note that some molecules of p53 itself can transfer into mitochondria and the process is accompanied with cytochrome *c* leaving mitochondria (bcl-2 prevented such effects) [34]. Interaction between p53 and MAPK-cascade that took place during cell cycle regulation was also described. It was established that p53 played certain role in necrosis initiation under direct interaction with cyclophilin D (CYPD), a mitochondrial matrix protein and a component in mitochondrial pore [1]. Vanadium is able to release Ca^{2+} from intracellular depots and its concentrations contribute significantly into regulation of mitochondrial pore opening [7]. Mitochondria and endoplasmatic reticulum are considered capacitive calcium depots. A change in calcium contents in a cell results in various cellular mechanisms being activated or inhibited including cell death mechanism. Vanadium (V) oxide V_2O_5 accumulated in mitochondrial lysosomes and stimulated autophagy in breast cancer (MCF-7) cells [14]. It was revealed via experiments that, depending on exposure duration, vanadium oxide both caused pro-oxidant effects and stimulated anti-oxidant properties in MCF-7 cells culture. Mitochondria play a key role in control over cellular calcium homeostasis and ROS generation and it means that mitochondria participate in regulation of various cell death types. It is in mitochondria that a cell «makes a choice» on a lethal program it is going to follow (apoptosis or necrosis). Apoptosis is initiated in case there is moder-

ate damage done to mitochondria membranes whereas considerable damage results in a cell dying via necrosis.

Vanadium is an element that can be in different oxidation states and that participates in reactions resulting in free radicals occurrence. Free radicals, regardless of their origin and reasons that caused their generation, can interact with nucleic acids, proteins, lipids, and carbohydrates. Cellular dysfunction caused by oxidative stress is often linked to damage to DNA and it can cause cell death. The International Agency on Cancer Research (IARC) experts consider that vanadium pentoxide belongs to 2B category or «is probably carcinogenic for people». It was shown in *in vivo* system that vanadium tore apart certain DNA threads, caused chromosome aberrations (structural and numerical) and nitrogen bases oxidation [35]. In a normal state genetically defective cells are to be eliminated via apoptosis. There is a hypothesis that insufficient apoptosis results in malignant transformation of damaged cells and tumor dissemination. There was an experiment performed on human hepatocellular carcinoma cells; it revealed that vanadium caused damage to nuclear and mitochondrial DNA and reduced cell vital capacity [36]. Mediated negative effects produced by vanadium on DNA as a result of reactive oxygen species generation involved desoxyribose oxidation, nitrogen bases modification, chains sewing together and tearing up. However, other researchers didn't believe vanadium had any carcinogenic properties [22, 37]. Depending on a suggested experimental model, vanadium concentrations and other vanadium-containing chemical compounds can have either anti-tumor or carcinogenic properties [21, 38]. Obviously, a key role in carcinogenesis occurrence belongs to cells being insusceptible to apoptosis or this process being inhibited.

Vanadium and its compounds inhibit activity of H^+,K^+-ATPhase, Na^+,K^+-ATPhase, and Ca^{2+},Mg^{2+}-ATPhase. Depending on ATPhase type, there can be a wide range of their affinity with vanadate [39]. It was shown that decavanadate $[V_{10}O_{28}]^6$ was the most powerful Ca^{2+}-ATPhase inhibitor in comparison with other vanadates [40]. ATPhases are most significant regulators of multiple cell functions including cell death [41]. In particular, non-apoptotic cell death (autosis) critically depends on Na^+,K^+-ATPhase activity [1]. ATPhases were proven to have a signal function. For example, a direct interaction between sodium-potassium ATPhase (Na^+,K^+-ATPhase) and Src-family kinase initiate phosphorilation of certain signal cascades that control cell death. It was established that metavanadate and ortovanadate inhibited Na^+,K^+-ATPhase in neuronal cells obtained from rat hippocampus [38].

The fact that vanadate is able to replace phosphate indicates that these two substances are similar to each other. Many benign or adverse effects produced by vanadate are at least partially due to similarities between these two anions. Vanadate and phosphate are groups with tetrahedral morphology and a charge almost spherically distributed in the outer sphere. Therefore, vanadate can easily replace phosphate in such enzymes as phosphatases and kinases [8]. However, an overall ionic charge of basic particles that occur at pH 7 is different as it is equal to 2 in phosphate and 1 in vanadate; it can result in different interactions with elecrophilic groups. Lower *d* orbital and a coordination number exceeding 4, usually 5 and 6, leads to one-electron vanadate recovery. As a result there is a growth in fixation of vanadates with side chains consisting of amino acid protein remnants [42]. There is a peculiarity vanadate has in physiologically significant concentrations and it makes it different from phosphate; this peculiarity is protonation state: at pH7 vanadate almost exclusively occurs in its diprotonated form whereas phosphate occurs as a mixture of mono- and dihydrophosphate [8]. Therefore, vanadate can easily replace phosphate in such enzymes as phosphates and kinases. In case vanadium occurs in a body in excess quantities, a change in enzyme cas-

cades activity in a cell results in a change in apoptotic signal conductivity.

Protein kinases (phosphotrasferases and kinases) and phosphatases are enzymes that accordingly catalyze phosphorilation (phosphate group addition) and de-phosphorilation (phosphate group removal) of a substrate. Under exposure to vanadium enzymes that participate in phosphate group transfer are inhibited or activated as a result of «vanadate – phosphate antagonism». Vanadate, due to its stronger bonding with phosphate-containing enzymes, is able to induces changes in activity of phosphorilation / de-phosphorilation enzymes. Kinases and phosphatases are responsible for activity of signal pathways that activate physiological effects cascade; due to this ability these enzymes are responsible for cell responses regulation. Imbalance between phosphorilation and de-phosphorilation can have negative influence on processes that are vital for cells functioning including cell survival or death. Experiments allowed establishing that vanadate inhibited phosphatases activity [43]. But at the same time vanadate is not a specific inhibitor for all phosphatases as it is still unclear how vanadium-containing chemical complexes inhibit many enzymes that catalyze substrate phosphorilation [7]. It was shown that oxovanadium (IV) complex (Na2[VO(Glu)2 (CH3OH)] (Glu=glutamate)) in concentration ranging from 0.21 to 0.37 μM inactivates protein tyrosine phosphatase 1B (PTP1B) [44]. PTP1B, as a negative regulator of insulin signal pathway, interacts directly with insulin receptor and de-phosphorilates tyrosine remnants [3]. Super-expression of this enzyme was detected in case of HER2-positive cancer. Protein tyrosine phosphatase 1B indirectly potentiates Src activity (cytosolic tyrosine kinase that is not bound to receptor). Certain vanadium compounds, pervanadates in particular, have oxidative properties in low concentrations and therefore they can directly activate Src [45]. Src-kinases are able to inhibit caspase-8 protease activity [46]. In case caspases are inactivated, FASL can initiate cell death as per necrosis type. As vanadium changes Na^+,K^+-ATPhase activity, it exerts indirect influence on Src. Src-kinase in an active component in activation of transcription factors such as AP-1 and NF-kB as well as mitogen-activated protein kinases (MARK-kinases) and membrane-bound proteins (Ras) that participate in transferring Ras/MAPK-signal cascade signals. Signal is transferred from cellular membrane to nucleus via Ras/MAP-kinase pathway activation thus influencing expression of a wide range of genes. Such activation of protein kinase signal pathways results in changes in protein products synthesis, mitochondria functional activity etc. [47]. Ras is also a component in multi-protein complex that regulates opening of mitochondrial membrane pores. When this complex is being formed, Ras molecules come from cytoplasm whereas proteins belonging to BCL-2family come from inside. Vanadium changes balance between pro- and anti-apoptotic members of BCL-2 family, disrupts functional activity of MAP-kinase cascades and transcription factors, and also increases generation of reactive oxygen species; in other words, it modifies cell death mechanisms and therefore plays a significant role in cell life cycle regulation.

Vanadium and its compounds cause imbalance in «oxidation – anti-oxidation» system via ROS formation. Reactive oxygen species are a key segment in initiating intracellular signal transduction and signal transfer in separate molecules thus making significant changes into MAP-kinase cascades activity. When MEK, ERK1/2, PI3K, p38, or JNK phosphorilation is modified (activated or inhibited) by vanadium, it modifies apoptosis start-up and development [35]. It was proven that intracellular protein p53 influenced activation or inactivation of MEK, ERK1/2, PI3K, p38, JNK, TNF-alpha, and NF-κB [48]. Molecular restructuring in PI3K and MAPK cascades under exposure to vanadium causes changes in cells survivability. Due to inhibited signal transfer through PI3K/Akt/mTOR cascade FAS-mediated apoptosis is induced [49]. Phosphatidylinositol-3-kinase (PI3K) activity

directly correlated with calcium ions concentration. CD95 doesn't have any enzyme activity; however, it can activate various signal pathways due to its ability to create interprotein (protein-protein) interactions [50]. FAS-induced signal cascades lead to NF-κB and MARK activation, apoptosis or necrosis initiation [51]. An immune-modulating effect produced by ERK1/2 which is phosphorilated close to cellular membrane involves B-lymphocytes and T-lymphocytes activation [52]. CD25-receptor is early T-lymphocytes activation marker; CD95-receptor, their late activation.

Research works that involved use of MEK1/2 kinases pharmacological inhibitors allowed proving that ERK1/2 participated in modifying functions performed by mitochondria that participated in apoptotic cascade amplification and regulation. Activation of protein kinases that belong to ERK family is most frequently associated with cells survival and proliferation stimulation. ERK protein kinases make for cellular cycle advancing as they inactivate protein kinase MYTI, one of its inhibitors. ERK signal pathways can be activated as a response to signals coming from receptors bound to G-protein via receptor tyrosine kinase, T-cellular receptor, N-methyl-D-aspartate receptor and C-type lectins receptors [52]. A set of signal cascades creates a network where ERK signal pathway communicates with various signal pathways via multiple branchings and collaterals, and it is regulated as per feedback principle and kinase-substrate ratio [52].

Some researchers described anti-apoptotic effects produced by ERK1/2 whereas others mentioned pro-apoptotic ones [7, 53]. As experiment performed on cells with melanoma origin (A375) showed that certain vanadium compounds (non-organic anion vanadate (V) and oxovanadium (IV) complex [VO (1.2-dimethyl-3-hydroxy-4(1)H)-pyridine nonate)$_2$]) in different concentrations (4.7 and 2.6 μM accordingly) induced cell apoptosis and cellular cycle stop. A375 line cells were treated with these vanadium-containing compounds (four- and five-valent vanadium) and it inhibited ERL phosphorilation by approximately 80 % together with inducing MAPK-cascade kinases inactivation [54]. Anti-tumor effects produced by vanadium on melanoma cells are determined by its ability to induce apoptosis via ROS generation. Experiments allowed establishing that when vanadium (V^{5+}) was added into cellular culture in quantity equal to 100 μmol/L^{-1}, it reduced vital capacity of epithelial oviduct cells. Meanwhile, treatment of cultivated SB203580 cells (p38 MAPK inhibitor) and U0126 cells (ERK1/2 inhibitor) eliminated apoptosis-inducing effects produced by vanadium [48]. Incubation of epithelial oviduct cells with MAPK inhibitors increased catalase and glutathione peroxidase activity (up to 89 %) as well as prevented increase in malonic dialdehyde concentration. It was shown that oxidative stress in epithelium oviduct cells caused by vanadium was partially due to p38 MAPK and JNK/Nrf2 activation that reduced expression of the 2nd phase detoxification enzymes. MEK/ERK signal cascade regulates expression of bcl-2 that prevents occurrence of transmembrane pores in mitochondria [55]. ROS, acting indirectly via ERK1/2, can activate caspase-3 and increase bak and bax expression. When activated, ERK1/2 and JNK kinases are able to participate in coordinating Keap1/Nrf2/ARE redox-sensitive signal system functioning. It was shown that p38 MAK and JNK stimulation exerted anti-apoptotic impacts in most cases. It was established that JNK was activated with FAS in many cell types [56]. But at the same time only long-term JNK activation provides an opportunity for apoptosis initiation and occurrence. An experiment revealed that p38 MAPK signal cascade was involved in regulation of p53, NF-κB, Stat1 transcription factors as well as bcl-2, Cdc25A apoptosis mediators [56]. It was proven that p38 MAPK and JNK participated in regulating FAS/FASL-system activity. p38 MAPK plays a significant role in regulating early expression of FASL and FAS-mediated caspases activation. Activated caspases stimulate JNK for further growth in FASL expression [57].

Analytical review of Russian and foreign scientific works has revealed that at present significant data have been accumulated on modifying effects produced by vanadium on apoptosis programs activation. Meanwhile multiple issues related to probable new ways for vanadium inducing or changing cell death processes remain disputable. Some researchers showed that vanadium had apoptosis-inducing properties and was able to initiate necrosis [54, 58–60]. However, other experts proved that vanadium was able to inhibit apoptosis [61]. But at the same time nowadays most experts in medical and biological sciences adhere to an opinion that apoptosis is the primary cell death way under exposure to vanadium [35]. But here we should clarify that most research works that focused on examining modifying effects produced by vanadium on apoptosis mechanisms were performed on tumor cells lines.

Oxovanadium in concentrations from 0.1 to 5.0 mg/kg reduced FAS-dependent apoptosis in *in vivo* system [61]. SOV (sodium ortovanadate) which inhibits tyrosine phosphoproetin phosphatases inhibited apoptosis of oral squamous cell carcinoma (Cal27) cells and inhibition was dose-dependent [60]. When natural killers (NK-92MI) were exposed to V_2O_5, it resulted in FAS, FASL, and CD25 hyper-expression. Vanadium-initiated lipid peroxidation in membrane makes for a change in membrane receptors expression. An increase in FAS-ligand quantity was registered under vanadium pentoxide concentration equal to 50 mM; maximum CD95-anmtigen expression was detected at its concentration being 100 mM; CD25-antigen, 400 mM [49]. It was shown that exposure to complex vanadium (IV) compounds resulted in inhibiting FAS-mediated apoptosis caused by protein kinase B (PKB) phosphorilation [48]. There was imbalance between anti-apoptotic and pro-apoptotic members of BCL-2 protein family, c-fos oncoprotein activation, poly (ADP-ribose) polymerase-1 disintegration and dose-dependent apoptosis activation when human epidermal keratinocytes were exposed to vanadyl sulfate (HaCaT) [62]. Vanadium ability to initiate receptor-dependent and p53-regulated apoptotic signal in a cell was shown in experiments performed on cellular lines. Greater initiating caspases-8 activity in mice fibrosarcoma (L929) cells and greater p53 expression in human hepatocellular carcinoma (HepG2) resulted from vanadium (IV) being added to the cell cultures [59]. Vanadium stimulated reactive oxygen species occurrence and thus induced autophagy, necroptosis, and mitotic disaster in a cell line of metastatic pancreatic adenocarcinoma (AsPC-1) [63]. Vanadium in an exposure dose equal to 0.0005 μg/cm^3 caused cell death as per necrosis type in *in vitro* system (leukocytes suspension obtained from peripheral blood of practically healthy children exposed to vanadium). Vanadium pentoxide nanoparticles (30–60 nm) inhibited proliferation of melanoma cells (B16F10), lung carcinoma cells **(**A549), and pancreatic carcinoma cells **(**PANC1). V_2O_5, internalization generated ROS inside cells, activated p53 protein and inhibited survivin in cancer cells thus inducing apoptosis. However there were no apparent cytotoxic effects produced by vanadium on normal cells (fibroblastic kidney cells NRK-49F, cells obtained from human embryo cells HEK 293, cell culture obtained from Chinese hamster ovaries CHO-K1) [64]. Obviously, modifying effects produced by vanadium on cell death depend on many components such as vanadium oxidation rate, exposure dose, exposure duration, cells species and cells belonging to a specific organ, differentiation stage, maturity stage, and cell functional state; it requires relevant interpretation of obtained results [13, 21, 27, 36, 44, 54, 58, 60].

In order to get a complete insight into modifying effects produced by vanadium on apoptosis, it is necessary to accomplish further profound research on cell death mechanisms taking into account fundamental regularities in the process as well as apoptosis peculiarities determined by the hapten influence. In order to extrapolate impacts exerted by vanadium on a healthy body, in future it

will be necessary to experimentally model apoptosis not only on tumor cells but also to more widely involve cells or cell lines taken from a healthy body to be used in *in vitro* systems. Probably, a small range of vanadium concentrations between its essentiality and toxicity predetermines multi-directional changes in apoptosis induction and completion [16, 38]. Moreover, peculiarities of an object (body) exposed to vanadium are also to be taken into account (age, sex, genetic peculiarities if xenobitoics metabolism, etc.) [3, 4, 7, 8, 31–33, 37, 48, 62, 63]. A hypothetic cell death mechanism modified by technogenic vanadium compounds is given in the Figure.

Control over cells population in a multicellular organism is a vital biological process that provides an opportunity for a body to get rid of potentially hazardous cells. Apoptosis activation makes for auto-immune and immune-proliferative processes development; cell death inhibition can result in immune deficiency, inflammatory reactions, and neurodegenerative diseases. Disorders in cell death become more probable under exposure to chemicals that pollute the environment. Environmental contamination with vanadium and its compounds due to technogenic activities create hazards for exposed adults' and children's health and this fact is truly alerting. Hazards caused by vanadium are predetermined by its ability to modify apoptosis mechanisms. Thus, vanadium-induced lipid peroxidation that has chain character results in changes in biophysical properties of membranes (greater permeability and changes in their fluidity), free radicals accumulation, and changes in membrane reception. Inside cells, vanadium and its compounds can also stimulate free oxygen species occurrence when metabolic reactions are developing in various cellular compartments. ROS produce their effects on separate protein molecules acting as inhibitors or activators and influence biochemical and physiological mechanisms of intracellular signalization. Immune-modifying effects produced by vanadium are related to blocking / activating enzymes via creating complexes with their substrates and via competing with phosphate in phosphate-binding

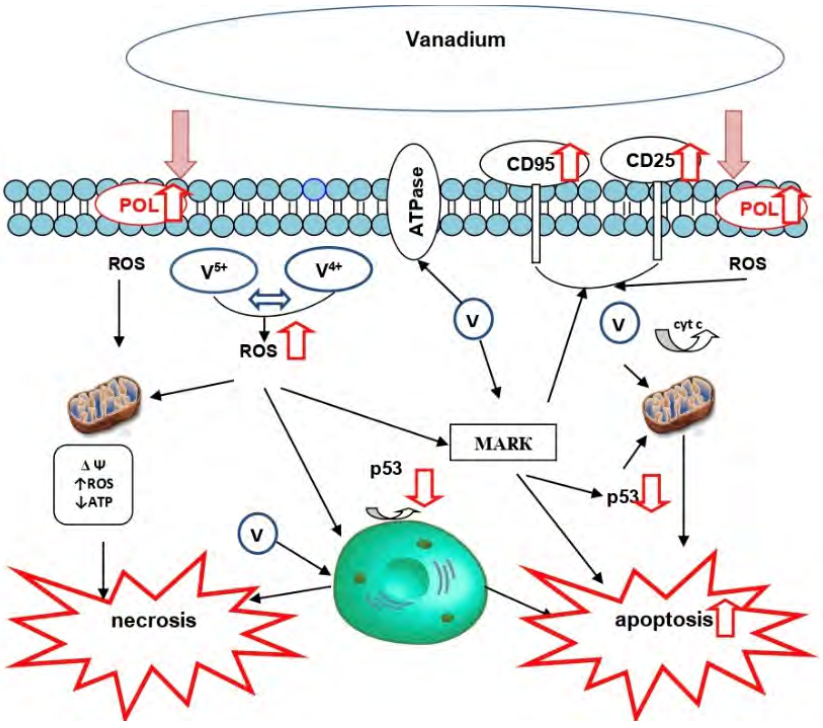

Figure. A hypothetic cell death mechanism modified by technogenic vanadium compounds; POL is lipid peroxidation, MARK are mitogen-activated protein kinase cascades; ROS are reactive oxygen species; *cyt c* is cytochrome *c*; ΔΨ is mitochondrial potential collapse

enzymes; ultimately, it induces changes in sections of intracellular transmission cascades [9]. Obviously, vanadium has significant immunetherapeutic potential since it is able to modify processes that result in cell life or death; it predetermines significance of further examination and analysis of molecular mechanisms and signal cascades under exposure to a hapten (vanadium). Monitoring over biological parameters that determine cell death under exposure to vanadium and its compounds provides an opportunity to timely identify risks of disease occurrence and prevent damage to health. The performed analysis of scientific works allowed revealing peculiarities and determining probable cell death scenarios under exposure to technogenic vanadium and its compounds.

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References

1. Galluzzi L., Vitale I., Aaronson S.A., Abrams J.M., Adam D., Agostinis P., Alnemri E.S., Altucci L. [et al.]. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell. Death & Differentiation,* 2018, vol. 25, no. 3, pp. 486–541. DOI: 10.1038/s41418-017-0012-4

2. Galluzzi L., Bravo-San Pedro J.M., Vitale I., Aaronson S.A., Abrams J.M., Adam D., Alnemri E.S., Altucci L. [et al.]. Essential versus accessory aspects of cell death: recommendations of the NCCD 2015. *Cell. Death & Differentiation*, 2015, vol. 22, no. 1, pp. 58–73. DOI: 10.1038/cdd.2014.137

3. Zwolak I. Protective effects of dietary antioxidants against vanadium-induced toxicity: A Review. *Oxid. Med. Cell. Longev*, 2020, vol. 7, no. 2020, pp. 1490316. DOI: 10.1155/2020/1490316

4. Li J., Jiang M., Zhou H., Jin P., Cheung K.M.C., Chu P.K., Yeung K.W.K. Vanadium dioxide nanocoating induces tumor cell death through mitochondrial electron transport chain interruption. *Global Challenges*, 2019, vol. 3, no. 3, pp. 1800058. DOI: 0.1002/gch2.201800058

5. Scalese G., Machado I., Correia I., Pessoa J.C., Bilbao L., Perez-Diaz L., Gambino D. Exploring oxidovanadium (IV) homoleptic complexes with 8-hydroxyquinoline derivatives as prospective antitrypanosomal agents. *NJC*, 2019, no. 45, pp. 17756–17773. DOI: 10.1039/c9nj02589h

6. Rehder D. Vanadium. Its role for humans. *Met. Ions Life Sci*, 2013, no. 13, pp. 139–169. DOI: 10.1007/978-94-007-7500-8_5

7. Treviño S., Díaz A., Sánchez-Lara E., Sanchez-Gaitan B.L., Perez-Aguilar J.M., González-Vergara E. Vanadium in biological action: chemical, pharmacological aspects, and metabolic implications in diabetes mellitus. *Biol. Trace. Elem. Res*, 2019, no. 188, pp. 68–98. DOI: 10.1007/s12011-018-1540-6

8. Rehder D. The role of vanadium in biology. *Metallomics,* 2015, no. 7, pp. 730–742. DOI: 10.1039/C4MT00304G

9. Vorob'eva N.M., Fedorova E.V., Baranova N.I. Vanadium: Its biological role, toxicology, and pharmacological applications. *Biosfera*, 2013, vol. 5, no. 1, pp. 77–96 (in Russian).

10. Dolgikh O.V., Zaitseva N.V., Dianova D.G. Regulation of apoptotic signal by strontium in immunocytes. *Biochemistry (Moscow) Supplement Series A: Membrane and Cell Biology*, 2016, vol. 10, no. 2, pp. 158–161. DOI: 10.1134/S1990747816010049

11. Alquezar C., Felix J.B., McCandlish E., Buckley B.T., Caparros-Lefebvre D., Karch C.M., Golbe L.I., Kao A.W. Heavy metals contaminating the environment of a progressive supranuclear palsy cluster induce tau accumulation and cell death in cultured neurons. *Scientific Reports*, 2020, vol. 10, no. 569, pp. 12. DOI: 10.1038/s41598-019-56930-w

12. Khorsandi K., Kianmehr Z., Hosseinmardi Z., Hosseinzadeh R. Anti-cancer effect of gallic acid in presence of low level laser irradiation: ROS production and induction of apoptosis and ferroptosis. *Cancer Cell. Int*, 2020, vol. 20, no. 18, pp. 18. DOI: 10.1186/s12935-020-1100-y

13. Dianova D.G., Dolgikh O.V. Exposure of vanadium as a factor of adverse activation of lymphocytes. *Ural'skii meditsinskii zhurnal*, 2012, vol. 102, no. 10, pp. 78–80 (in Russian).

14. Suma P.R.P., Padmanabhan R.A., Telukutla S.R., Ravindran R., Velikkakath A.K.G., Dekiwadia C.D., Paul W., Shenoy S.J. [et al.]. Paradigm of Vanadium pentoxide nanoparticle-induced autophagy and apoptosis in triple-negative breast cancer cells. *bioRxiv*, 2019, no. 18, pp. 33. DOI: 10.1101/810200

15. MacGregor J.A., White D.J., Williams A.L. The limitations of using the NTP chronic bioassay on vanadium pentoxide in risk assessments. *Regul. Toxicol. Pharmacol.*, 2020, no. 113, pp. 104650. DOI: 10.1016/j.yrtph.2020.104650

16. Adam M.S.S., Elsawy H. Biological potential of oxo-vanadium salicylediene amino-acid complexes as cytotoxic, antimicrobial, antioxidant and DNA interaction. *J. Photoch. Photobio. B.*, 2018, no. 184, pp. 34–43. DOI: 10.1016/j.jphotobiol.2018.05.002

17. Fedorova E.V., Buryakina A.V., Vorob'eva N.M., Baranova N.I. The vanadium compounds: chemistry, synthesys, insulinomimetic properties. *Biomeditsinskaya khimiya*, 2014, vol. 60, no. 4, pp. 416–429 (in Russian).

18. Ma J., Pan L.B., Wang Q., Lin C.Y., Duan X.L., Hou H. Estimation of the daily soil/dust (SD) ingestion rate of children from Gansu Province, China via hand-to-mouth contact using tracer elements. *Environ. Geochem. Health*, 2018, vol. 40, no. 1, pp. 295–301. DOI: 10.1007/s10653-016-9906-1

19. Eqani S.A.M.A.S., Tanveer Z.I., Qiaoqiao C., Cincinelli A., Saqib Z., Mulla S.I., Ali N., Katsoyiannis I.A. [et al.]. Occurrence of selected elements (Ti, Sr, Ba, V, Ga, Sn, Tl, and Sb) in deposited dust and human hair samples: implications for human health in Pakistan. *ESPR,* 2018, vol. 25, no. 13, pp. 12234–12245. DOI: 10.1007/s11356-017-0346-y

20. Pyatikonnova A.M., Pozdnyakov A.M., Sarkitov Sh.S. Toksicheskoe deistvie vanadiya i ego soedinenii [Toxic effects produced by vanadium and its compounds]. *Uspekhi sovremennogo estestvoznaniya*, 2013, no. 9, pp. 120 (in Russian).

21. Korbecki J., Baranowska-Bosiacka I., Gutowska I., Chlubek D. Biochemical and medical importance of vanadium compounds. *Acta. Biochim. Pol*., 2012, vol. 59, no. 2, pp. 195–200.

22. Toxicological review of vanadium pentoxide (V_2O_5) (CAS No. 1314-62-1). In Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC, U.S. Environmental Protection Agency Publ., 2011, 210 p.

23. Scior T., Guevara-Garcia J.A., Do Q.T., Bernard P., Lauferd S. Why antidiabetic vanadium complexes are not in the pipeline of «big pharma» drug research? A Critical Review. *Curr. Med. Chem.*, 2016, vol. 23, no. 25, pp. 2874–2891. DOI: 10.2174/0929867323666160321121138

24. Sanna D., Serra M., Micera G., Garribba E. On the transport of vanadium in blood serum. *Inorg. Chem*, 2009, vol. 48, no. 13, pp. 5747–5757. DOI: 10.1021/ic802287s

25. Sanna D., Serra M., Micera G., Garribba E. Speciation of potential anti-diabetic vanadium complexes in real serum samples. *J. Inorg. Biochem,* 2017, no. 173, pp. 2–65. DOI: 10.1016/j.jinorgbio.2017.04.023

26. Sanna D., Ugone V., Sciortino G., Buglyó P., Bihari Z., Parajdi Losonczi P.L., Garribba E. Vivo complexes with antibacterial quinolone ligands and their interaction with serum proteins. *Dalton Trans*, 2018, vol. 47, no. 7, pp. 2164–2182. DOI: 10.1039/c7dt04216g

27. Rehder D. The (Biological) Speciation of Vanadate (V) as Revealed by 51V NMR – A Tribute on Lage Pettersson and His Work. *J. Inorg. Biochem*, 2015, vol. 147, pp. 25–31. DOI: 10.1016/j.jinorgbio.2014.12.014

28. Wang L., Medan D., Mercer R., Overmiller D., Leornard S., Castranova V., Shi X., Ding M. [et al.]. Vanadium-induced apoptosis and pulmonary inflammation in mice: role of reactive oxygen species. *J. Cell. Physiol*, 2003, vol. 195, no. 1, pp. 99–107. DOI: 10.1002/jcp.10232

29. Jiang Q.Y.W., Li D., Gu M., Liu K., Dong L., Wang C., Jiang H., W Dai. Sodium orthovanadate inhibits growth and triggers apoptosis of human anaplastic thyroid carcinoma cells in vitro and *in vivo. Oncol. Lett*, 2019, vol. 17, no. 5, pp. 4255–4262. DOI: 10.1016/S0168-8278(00)80101-4

30. Irving E., Stoker A.W. Vanadium compounds as PTP inhibitors. *Molecules*, 2017, vol. 22, no. 12, pp. 2269. DOI: 10.3390/Molecules22122269

31. Hosseini M.-J., Shaki F., Ghazi-Khansari M., Pourahmad J. Toxicity of vanadium on isolated rat liver mitochondria: A new mechanistic approach. *Metallomics*, 2013, vol. 5, no. 2, pp. 152–156. DOI: 10.1039/c2mt20198d

32. Cunha-de Padua M.M., Cadena S.M.S.C., Petkowicz C.L.O., Martinez G.R., Merlin-Rocha M., Merce A.L., Noleto G.R. Toxicity of native and oxovanadium (IV/V) galactomannan complexes on HepG2 cells is related to impairment of mitochondrial functions. *Carbohydrate Polymers*, 2017, vol. 1, no. 173, pp. 665–675. DOI: 10.1016/j.carbpol.2017.06.027

33. Zhao Y., Ye L., Liu H., Xia Q., Zhang Y., Yang X., Wang K. Vanadium compounds induced mitochondria permeability transition pore (PTP) opening related to oxidative stress. *J. Inorg. Biochem*, 2010, vol. 104, no. 4, pp. 371–378. DOI: 10.1016/j.jinorgbio

34. Dyatlova A.S., Dudkov A.V., Lin'kova N.S., Khavinson V.Kh. Molecular markers of caspase-dependent and mitochondrial apoptosis: the role of pathology and cell senescence. *Uspekhi sovremennoi biologii*, 2018, vol. 138, no. 2, pp. 126–137 (in Russian).

35. Rojas-Lemus M., Bizarro-Nevares P., López-Valdez N., González-Villalva A., Guerrero-Palomo G., Cervantes-Valencia M.E., Tavera-Cabrera O., Rivera-Fernández N. [et al.]. Oxidative stress and vanadium. *IntechOpen*, 2020. Available at: https://www.intechopen.com/online-first/oxidative-stress-and-vanadium (29.09.2020).

36. Rivas-García L., Quiles J.L., Varela L.A., Arredondo M., Lopez P., Dieguez A.R., Aranda P., Llopis J. [et al.]. In vitro study of the protective effect of manganese against vanadium-mediated nuclear and mitochondrial DNA damage. *Food and Chemical Toxicology*, 2019, no. 135, pp. 110900. DOI: 10.1016/j.fct.2019.110900

37. Starr T.B., Macgregor J.A., Ehman K.D., Kikiforov A.I. Vanadium pentoxide: Use of relevant historical control data shows no evidence for carcinogenic response in F344/N rats. *Regul. Toxicol. Pharmacol.*, 2012, vol. 64, no. 1, pp. 155–160. DOI: 10.1016/j.yrtph.2012.06.017

38. Gruzewska K., Michno A., Pawelczyk T., Bielarczyk H. Essentiality and toxicity of vanadium supplements in health and pathology. *J. Physiol. Pharmacol*, 2014, vol. 65, no. 5, pp. 603–611.

39. Marques M.P.M., Gianolio D., Ramos S., Batista de Carvalho L.A.E., Aureliano M. An EXAFS Approach to the Study of Polyoxometalate–Protein Interactions: The Case of Decavanadate–Actin. *Inorg. Chem.*, 2017, vol. 56, no. 18, pp. 10893–10903. DOI: 10.1021/acs.inorgchem.7b01018

40. Montes M.R., Spiaggi A.J., Monti J.L., Cornelius F., Olesen C., Garrahan P.J., Rossi R.C. Rb(+) occlusion stabilized by vanadate in gastric H(+)/K(+)-ATPase at 25°C. *Biochim. Biophys. Acta.,* 2011, vol. 1808, no. 1, pp. 316–322. DOI: 10.1016/j.bbamem.2010.08.022

41. He J., Xing J., Yang X., Zhang C., Zhang Y., Wang H., Xu X., Wang H. [et al.]. Silencing of proteasome 26S subunit ATPase 2 regulates colorectal cancer cell proliferation, apoptosis, and migration. *Chemotherapy*, 2019, vol. 64, no. 3, pp. 146–154. DOI: 10.1159/000502224

42. Turner T.L., Nguyen V.H., McLauchlan C.C., Dymon Z., Dorsey B.M., Hooker J.D., Jones M.A. Inhibitory effects of decavanadate on several enzymes and Leishmania tarentolae *in vitro. J. Inorg. Biochem.*, 2011, no. 108, pp. 96–104. DOI: 10.1016/j.jinorgbio.2011.09.009

43. McLauchlan C.C., Peters B.J., Willsky G.R., Crans D.C. Vanadium-phosphatase complexes: Phosphatase inhibitors favor the trigonal bipyramidal transition state geometries. *Coord. Chem. Rev.,* 2015, vol. 301–302, no. 15, pp. 163–199. DOI: 10.1016/j.ccr.2014.12.012

44. Lu L., Wang S., Zhu M., Liu Z., Guo M., Xing S., Fu X. Inhibition protein tyrosine phosphatases by an oxovanadium glutamate complex, Na2[VO(Glu)2(CH3OH)](Glu = glutamate). *Biometals*, 2010, vol. 23, no. 6, pp. 1139–1147. DOI: 10.1007/s10534-010-9363-8

45. Korbecki J., Baranowska-Bosiacka I., Gutowska I., Chlubek D. Vanadium compounds as pro-inflammatory agents: effects on cyclooxygenases. *Int. J. Mol. Sci.,* 2015, vol. 16, no. 6, pp. 12648–12668. DOI: 10.3390/ijms160612648

46. Gallo M.L., Poissonnier A., Blanco P., Legembre P. CD95/FAS, Non-apoptotic signaling pathways, and kinases. *Front. Immunol*, 2017, vol. 27, no. 8, pp. 1216. DOI: 10.3389/fimmu.2017.01216

47. Lingrel J.B. The physiological significance of the cardiotonic steroid/ouabainbinding site of the Na, K-ATPase. *Annu. Rev. Physiol.*, 2010, vol. 17, no. 72, pp. 395–412. DOI: 10.1146/annurev-physiol-021909-135725

48. Wang J., Huang X., Zhang K., Mao X., Ding X., Zeng Q., Bai S., Xuan Y. [et al.]. Vanadate oxidative and apoptotic effects are mediated by the MAPK-Nrf2 pathway in layer oviduct magnum epithelial cells. *Metallomics*, 2017, vol. 9, no. 11, pp. 1562–1575. DOI: 10.1039/c7mt00191f

49. Gallardo-Vera F., Diaz D., Tapia-Rodriguez M., Fortoul G.T., Masso F., Rendon-Huerta E., Montaño L.F. Vanadium pentoxide prevents NK-92MI cell proliferation and IFNγ secretion through sustained JAK3 phosphorylation. *J. of Immunotoxicol*, 2016, vol. 13, no. 1, pp. 27–37. DOI: 10.3109/1547691X.2014.996681

50. Guegan J.-P., Legembre P. Nonapoptotic functions of FAS/CD95 in the immuneresponse. *FEBS*, 2018, vol. 285, no. 5, pp. 809–827. DOI: 10.1111/febs.14292

51. Xiao K., Liu C., Tu Z., Xu Q., Chen S., Zhang Y., Wang X., Zhang J. [et al.]. Activation of the NF-κB and MAPK signaling pathways contributes to the inflammatory responses, but not cell injury, in IPEC-1 cells challenged with hydrogen peroxide. *Oxid. Med. Cell. Longev*, 2020, no. 2020, pp. 5803639. DOI: 10.1155/2020/5803639

52. Yang L., Zheng L., Chng W.J., Ding J.L. Comprehensive analysis of ERK1/2 substrates for potential combination immunotherapies. *Trends Pharmacol. Sci*, 2019, vol. 40, no. 11, pp. 897–910. DOI: 10.1016/j.tips.2019.09.005

53. Wortzel I., Seger R. The ERK cascade: distinct functions within various subcellular organelles. *Genes Cancer*, 2011, vol. 2, no. 3, pp. 195–209. DOI: 10.1177/1947601911407328

54. Pisano M., Arru C., Serra M., Galleri G., Sanna D., Garribba E., Palmieri G., Rozzo C. Anti-proliferative activity of vanadium compounds: effects on the major malignant melanoma molecular pathways. *Metallomics*, 2019, vol. 11, no. 10, pp. 1687–1699. DOI: 10.1039/C9MT00174C

55. Rodrıguez-Berriguete G., Fraile B., Martınez-Onsurbe P., Olmedilla G., Paniagua R., Royuela M. MAP kinases and prostate cancer. *J. Signal. Transduction*, 2012, no. 2012, pp. 169170. DOI: 10.1155/2012/169170

56. Misyurin V.A. Structure and functions of main apoptosis receptors and ligands. *Rossiiskii bioterapevticheskii zhurnal*, 2015, vol. 14, no. 2, pp. 23–30 (in Russian).

57. Zhang B.J., Gao J.-X., Salojin K., Shao Q., Grattan M., Meagher C., Laird D.W., Delovitch T.L. Regulation of FAS Ligand expression during activationinduced cell death in T cells by p38 mitogen-activated protein kinase and c-Jun NH2-terminal kinase. *J. Exp. Med*, 2000, vol. 191, no. 6, pp. 1017–1030. DOI: 10.1084/jem.191.6.1017

58. Jiang Q.Y.W., Li D., Gu M., Liu K., Dong L., Wang C., Jiang H., Dai W. Sodium orthovanadate inhibits growth and triggers apoptosis of human anaplastic thyroid carcinoma cells in vitro and *in vivo*. *Oncol. Lett,* 2019, vol. 17, no. 5, pp. 4255–4262. DOI: 10.3892/ol.2019.10090

59. Aliabad H.B., Falahati-Pour S.K., Ahmadirad H., Mohamadi M., Hajizadeh M.R., Bakhshi G., Mahmoodi M. Vanadium complex induced apoptosis in hepg2 cells by the up-regulation of p53, p21, and caspase-8. *WCRJ,* 2019, no. 6, pp. e1293. DOI: 10.32113/wcrj_20195_1293

60. Shioda N., Ishigami T., Han F., Moriguchi S., Shibuya M., Iwabuchi Y., Fukunaga K. Activation of phosphatidylinositol 3-kinase/protein kinase B pathway by a vanadyl compound mediates its neuroprotective effect in mouse brain ischemia. *Neuroscience*, 2007, vol. 148, no. 1, pp. 221–229. DOI: 10.1016/j.neuroscience.2007.05.040

61. Markopoulou S., Kontargiris E., Batsi C., Tzavaras T., Trougakos I., Boothman D.A., Gonos E.S., Kolettas E. Vanadium-induced apoptosis of HaCaT cells is mediated by c-fos and involves nuclear accumulation of clusterin. *FEBS J*, 2009, vol. 276, no. 14, pp. 3784–3799. DOI: 10.1111/j.1742-4658.2009.07093.x

62. Khalil A., Dzhemeson M. Sodium orthovanadate inhibits proliferation and triggers apoptosis in oral squamous cell carcinoma in vitro. *Biokhimiya*, 2017, vol. 82, no. 2, pp. 258–265 (in Russian).

63. Kowalski S., Wyrzykowski D., Hac S., Rychlowski M., Radomski M.W., Inkielewicz-Stepniak I. New oxidovanadium (IV) coordination complex containing 2-methylnitrilotriacetate ligands induces cell cycle arrest and autophagy in human pancreatic ductal adenocarcinoma cell lines. *IJMS*, 2019, vol. 20, no. 2, pp. 261. DOI: 10.3390/ijms20020261

64. Das S., Roy A., Barui A.K., Alabbasi M.M.A., Kuncha M., Sistla R., Sreedhar B., Patra C.R. Anti-angiogenic vanadium pentoxide nanoparticles for the treatment of melanoma and their in vivo toxicity study. *Nanoscale*, 2020, vol. 12, no. 14, pp. 7604–7621. DOI: 10.1039/d0nr00631a

Dolgikh O.V., Dianova D.G., Kazakova O.A. Vanadium in the environment as a risk factor causing negative modification of cell death (scientific review). *Health Risk Analysis, 2020, no. 4, pp. 155–168. DOI: 10.21668/health.risk/2020.4.18.eng*

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