Halogenated Compounds and Carcinogenesis: An Integrative Review ofTheir Role and Therapeutic Options

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Abstract

Halogenated compounds, a significant category of chemicals, have been identified as contributors to the development and progression of cancer inside the human body. The elimination of these compounds poses considerable challenges. Halogenated compounds encompass a range of chemical substances, such as vinyl chloride, carbon tetrachloride, hexachlorobenzene, trichloroethylene, brominated chemicals, and chloroform, among others. The scientific literature frequently discusses and examines the chlorinated and brominated derivatives of halogenated phenolic compounds. Each of these substances functions as both carcinogens and mutagens. In relation to industrial sources, the proportion of naturally occurring molecular halide compounds in the environment is considerably diminished, several processes, such as chemical oxidation, disinfection, and aggregation using chemicals that include chlorine (such as FeCl3), can be cited as examples. Various organs can be affected variably by these substances, potentially leading to the development of skin, thyroid gland, liver, testis, and respiratory system malignancies. From our understanding, no similar examination of human populations is provided. Additionally, no comparisons have been made between measured halogenated compound levels in individuals or animals and pertinent toxicology evidence. As more information comes in about how harmful

halogenated phenolic compounds are to cells, it is very important to look over the doses that were given and how they were thought to affect people. The objectives of this review entail the examination of reported tissue-specific halogenated compounds and their associated toxicity burdens in both human and animal subjects. The primary aim is to ascertain the relative abundance of these compounds in relation to their putative precursor chemicals, while establishing a correlation between these quantities and pertinent toxicity thresholds. Cancer always develops by causing changes in DNA, which, as a result, causes abnormal and uncontrolled production of cells in our body. This article discusses different types of halogenated compounds, their sources, their effects, the types of cancer they cause, how that particular cancer affects people, and whether there are sufficient therapy options to treat it.

Keywords: Halogenated compounds, toxicity, cancer, hexachlorobenzene (HCB), carcinogen, Treatment

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Introduction

Halogen organic compounds are synthesized when molecules belonging to the class of halogen elements attach to organic substances. These compounds are introduced into the atmosphere through both spontaneous and artificial processes. There are numerous natural processes that produce these compounds, including the burning of organic materials, flames, volcanic activity, and the fermentation of fungi, algal growth, sponges, and lichen species [1]. The amount of naturally occurring molecular halide compounds in the environment is significantly lower than that of anthropogenic activity like chemical oxidation, disinfection, and aggregation with chemicals having Cl (such as FeCl3). Indicators used to calculate the overall chemical composition of such substances within the atmosphere include: 1) AOX/NAOX, organic halogens that are adsorbable or non-adsorbable, 2) VOX/NVOX, organic halogens that are

volatile or non-volatile, 3) EOX, easily extracted organic halogen compounds; and 4) POX/NPOX, which constitute both extractable and non-extractable varieties of organic halogen compounds.

People are worried about aromatic halogen compounds (XAr) because they arefound in a lot of places and can cause cancer. This makes people wonder what health and environmental risks they might pose. Advanced processes for oxidation (AOPs) have recently gained favor as an "environmentally friendly" solution for treating these refractory and hazardous wastes. Ploy-halogenated Quinone's XBQs can produce a metal-independent hemolytic breakdown of H2O2, releasing a hydroxyl ion (OH-) as a byproduct. A very strong oxidizing radical called hydroxyl radical (•OH) can damage nucleophilic parts of genomic sequences right away. It is frequently referred to as the most reactive and harmful ROS [2].

$$H_2O_2 + Me^{(n-1)} \rightarrow HO + OH^- + Me^{n+}$$

Recently, a lot of poly-halogenated quinones, which might cause bladder cancer, were found in drinking water as new byproducts of chlorination [3]. It is known that XBQs/H2O2 can oxidize dsDNA, and that the metal-independent production of extremely reactive OH is what causes dsDNA direct oxidation. There is a significant difference between the oxidative power of XBQs/H2O2 and the traditional iron-regulated Fenton complex [4]. A new investigation explored if 1,2-dichloroethane DCE may cause malignancy by employing mouse models. A 26-week study that investigated the tumorigenicpotential of this organic compound using transgenic mice revealed that 1,2 dichloroethane is a respiratory carcinogen when applied topically to the dorsal epidermis. Every female mousewithin the rasH2 animal model either developed tumors within their alveoli and bronchioles or similar types of adenocarcinomas, proving that 1,2-dichloroethane is a potent respiratory carcinogen. When ingested by B6C3F1 mice, 1,2-dichloroethane causes uterine and breast cancers within female mice as well as hepatocellular carcinoma within male mice [5].

Causes (halogenated compounds causing cancer)

- Carbon tetrachloride.
- Hexachlorobenzene.
- Chloroform.
- Vinyl chloride.
- Poly brominated biphenyls.
- Chlorinated PAHs.
- Organic and inorganic brominated chemicals like DDT, PBB.
- Trichloroethylene.

Carbon Tetrachloride (CCl4)

Several genotoxicity and mutagenicity investigations have been conducted on carbon tetrachloride, and various reviews have been published on the subject. In microbial species, CCl4 has undergone rigorous and recurring testing to investigate its potential to inducengenetic modification and DNA breaks [6]. Studies have found that carbon tetrachloride ought not to be deemed to be a direct mutagenic agent adopting a weight of evidence methodology. If mutagenic effects occur, they are most likely caused by indirect processes caused by oxidative and lipid peroxidative assault.

Biologically activated carbon tetrachloride can be genotoxic in extremely cytotoxic conditions. These are often of minor magnitude and present largely as DNA breaks and accompanying consequences and to a lesser extent, chromosome loss may result in aneuploidy [7].

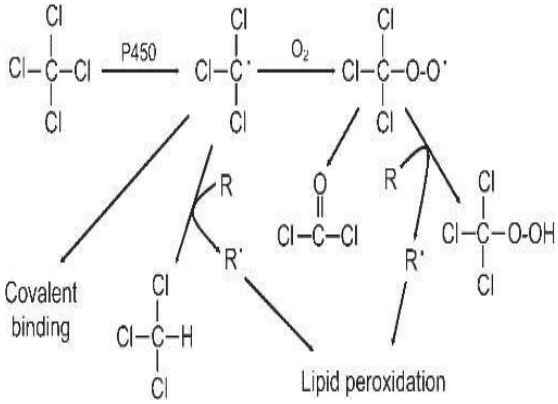
Carbon tetrachloride is responsible for the centric-lobular necrosis as well as the fat degeneration of the liver. Accumulation of lipids in the liver happens very early because of the inability of this organ (liver) to transport the low-density lipoproteins that are rich in triglyceride to the plasma. As seen in Fig. 1.0, CYP450 breaks down CCl4 into its chemical metabolite, trichloromethyl radical that is subsequently converted to a peroxy radical. Polyunsaturated fats and CCl4 compounds work together to start a cascade of reactions, which peroxidizes the fats or damages hepatocytes by binding chemically to polypeptides and triglycerides [8, 9].

Figure 1: *Key metabolic steps involved in the activation of carbon tetrachloride CCl4. R represents lipid-derived radical [10]*

Betaine as well as interferon could safeguard against the kidney damage caused by CCl4 in animal models, according to new research. Kidney damage is often observed a few days

after CCl4 contact in

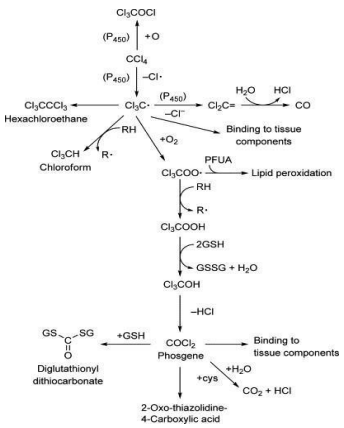
Figure 2: *Cytochrome P450 (CYP) 2E1 reduces CCl4 to trichloromethyl free radical (Cl3C radical dot), which in turn produces trichloromethyl peroxy free radical, phosgene, as well as glutathione carbonate [11].*



individuals and small mammals, compared to the rapid development of CCl4-induced liver damage that occurs just 24 hours after exposure. Elevated levels of urea nitrogen and creatinine within blood serum as well as proteinuria, anuria, or oliguria are signs of CCl4-induced kidney damage. It has been discovered that CYP2E1 converts CCl4 in rodent kidneys and liver to produce a trichloromethyl radical, which can then be oxidized to produce phosgene (Figure 2). When phosgene is hydrolyzed, CO2, a key metabolite of CCl4, is produced. It is also possible for the trichloromethyl radical to remove a hydrogen radical from unsaturated fatty acids to produce chloroform anda fatty acid radical, which can result in peroxidation of lipids. Additionally, fatty acids and proteins can establish covalent bonds with the trichloromethyl radical. Nevertheless, it is currently unknown how this metabolic reaction contributes to kidney damage caused by CCl4 [11].

Hexachlorobenzene (HCB)

Hexachlorobenzene is a synthetic chemical that is created by chlorine-treated benzene at temperatures between 150 and 200 degrees Celsius with the use of a catalytic reagent like FeCl3. Hexachlorobenzene acts as a common organochlorine insecticide in the environment. There are several effects of chronic exposure to HCB in humans, including the onset of porphyria, the induction of microsomal enzymes, hormonal disorders,



neurological manifestations, and immunological abnormalities. HCB causes porphyria by increasing the activity of d-aminolevulinic acid synthase (ALA-S) and decreasing the activity of uroporphyrinogen decarboxylase (UD). While UD converts uroporphyrinogen III to coproporphyrinogen III, the amount of porphyrin and heme produced is regulated by ALA-S. All four pyrrole rings' acetate side chains are decarboxylated by the cytosolic enzyme UD, which produces methyl residues in the process. Uroporphyrin III does not get further metabolized since HCB inhibits UD [12].

Hexachlorobenzene concentrations in tissues or blood have not been linked to the prevalence of malignancies in any particular locations, according to epidemiological research in the general population. The drawbacks of all of these investigations includesmall sample sizes and/or interactions with further organic chlorine compounds. The relationship involving HCB infection and malignancies, specifically testicular germ cell tumors, non-Hodgkin's lymphoma, malignancies of the prostate, as well as breast cancers, has been the subject of several epidemiological studies.

In research involving 159 breast carcinoma victims as well as 250 normal volunteers, blood HCB values were used to estimate the rate of infection. Following receiving a diagnosis of breast carcinoma and before starting therapy, blood specimens were collected. In 32% of instances, the threshold of quantification, established at 0.05 ng/ul for HCB in the bloodstream, was surpassed. Approximately 4% of healthy female participants exhibited HCB concentrations that were higher than the established threshold. An OR of 9.1 (95% CI: 2.8-29.4), indicating a higher incidence of developing breast cancer was associated with an elevated level of HCB [13].

In the rat mammary gland, HCB promotes insulin receptor substrate-1 (IRS-1) by boosting the transcription of IGF-1 receptors (IGF-1R), the body's next-generation growth factor. Additionally, HCB stimulates c-Src phosphorylation, causing interaction between c- Src and the ER and HER1 receptors. Such receptors then phosphorylate and stimulate numerous intracellular mediators, including the The rise in the number of lactation glands seen in mice models exposed to HCB may be due to HER1 signalling, which encourages axillary bifurcation of mammary glands signalling transducer and activator of transcription 5b (Stat5b) and the extracellular signal

related enzymes 1 and 2 (ERK1-2). [14].

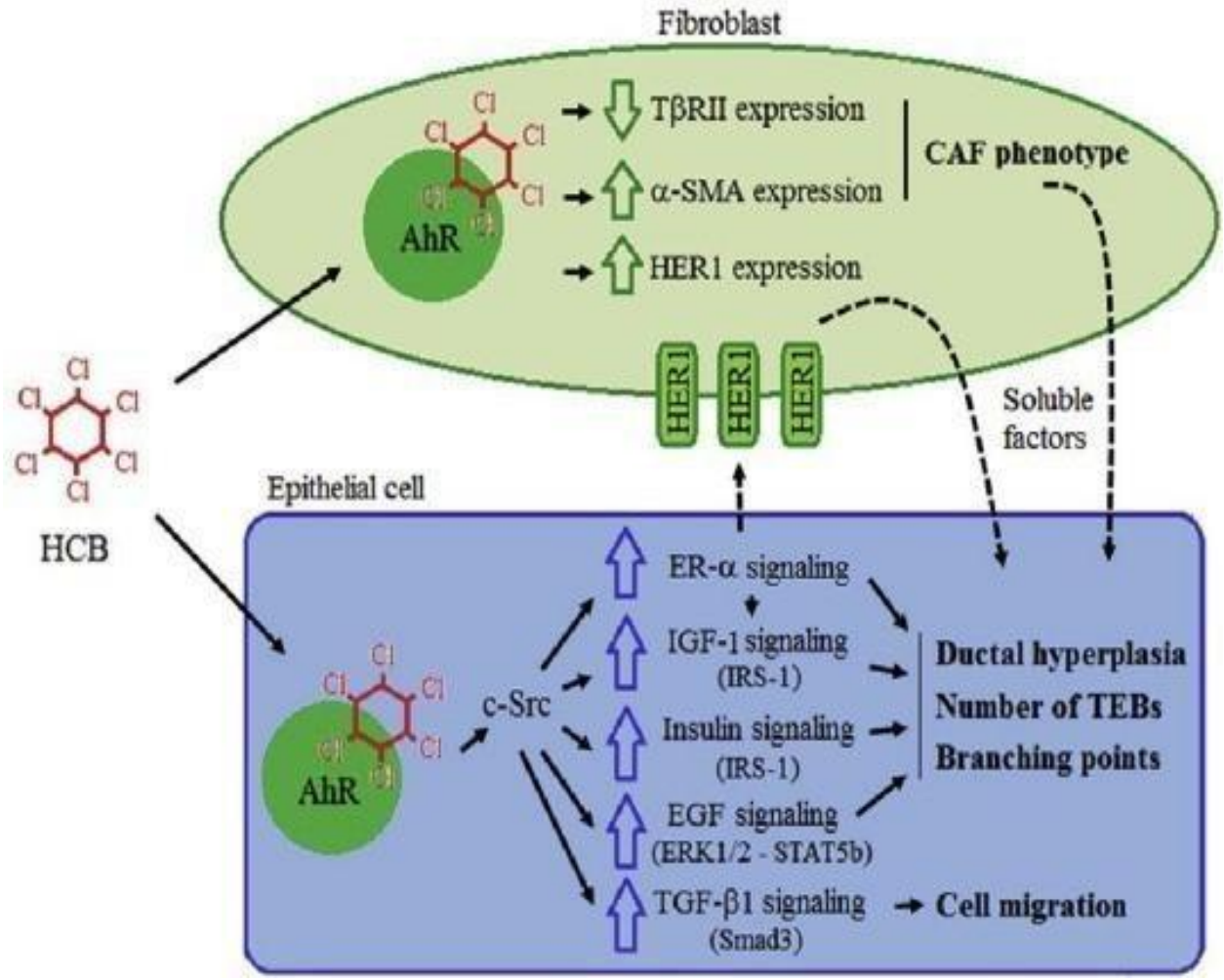


Figure 2: *Effect of HCB on mammary gland [15]. Inducing the growth of epithelial cells, ductal hyperplasia, and an increase in TEBs and branching points, HCB binds to AhR. These findings were elucidated through the stimulation of the AhR trans-membrane route, which is regulated by c-Src and promotes the signaling pathways for ER, IGF-1R, IR, as well as HER1 within the epithelium. The HER1 signaling cascade can be stimulated in fibroblasts upon ER activation in epithelial cells, which could ultimately promote the proliferation of epithelial cells. Additionally, HCB encourages TGF-1 signaling, which in turn improves epithelial cell motility. On the flip side, HCB causes fibroblasts to have a CAF-like phenotype by decreasing TRII levels while increasing -SMA. Due to the soluble substances these fibroblasts produce, epithelial cells migrate and undergo mammary gland change*.

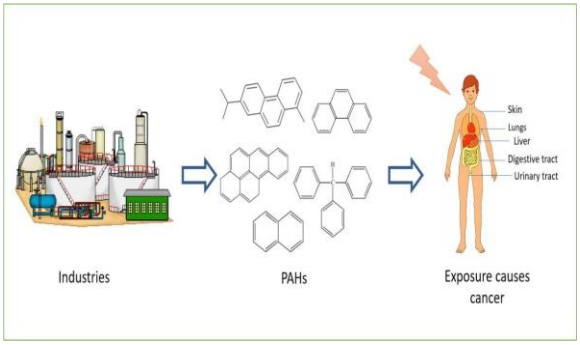
Chloroform

Chloroform, also known as trihalomethane (CHCl3) is considered the most dangerous carcinogenic agent found in water. It has been proven that the existence of CHCl3 in the environment can increase the risk of cancer development (especially in the case of hepatocellular, adrenal and renal carcinomas) more in animals (specifically rodents) as compared to humans. Various health authorities are signing protocols that would help decrease chloroform concentrations in tap water, but its existence in the air is being neglected as skin exposure and inhalation of chloroform also increases the cancer risk [16].

This happens because chloroform can undergo redox reactions inside the cells and tissues in the human

body. The liver metabolism rate is decreased by chloroform. When chloroform processes its oxidation, it gives rise to phosgene which in return reacts with the nucleophiles in tissues and makes covalent bonds. As a result, the depletion of glutathione in the liver occurs. Whereas the rate of kidney tumors is less as compared to the liver because the kidney, to some extent can metabolize the chloroform and get rid of it [17].

Figure 3: *Chloroform-induced cytotoxicity and its effects on cell repair, proliferation and celldeath [18]*



Trichloroethylene (TCE)

Trichloroethylene has been considered the best solvent for cleaning purposes andother industrial applications for decades. The International Agency for Research on Cancer claims that researchers have determined the correlation of TCE with various cancers, both lymphoma (kidney, liver, testes, and lungs) and leukemia; hence, its consumption has decreased over time. As TCE is in water and air, those who are more exposed to it will have a higher chance of developing a disease. To determine the level of TCE and TCA in the human body, we need to measure their toxicology in urine samples. Hence, urine is considered a biomarker to measure TCE levels in our body

[19, 22].TCE can be present in any solution and, when uptake by humans, can cause

cancer. Studies were conducted in which both male and female rats were exposed to TCE, and as a result, they developed renal tubular cancers in their lives [20, 21]. Because of this, trichloroethylene is thought to play a role in causing biliary tract infections, Hodgkin's disease, multiple myeloma, and cervical cancer [22].

Polycyclic Aromatic Hydrocarbons (PAHs)

Another important class of halogenated compounds causing cancer is the chlorinated and halogenated PAHs. They are very dangerous atmospheric pollutants and are formed by the pyrolysis of oils and petroleum fuels. Once they enter the human body or penetrate it, they can be found in every organ, like the skin, liver, lungs, and digestive tract, and can cause cancer. They have different sources like cigarette smoke, industries, dyes, pesticides, car exhaust, etc. They can even

Vinyl Chloride

Vinyl chloride monomer (VCM) is a sweet-smelling colourless gas that is mainly usedin PVC production for furnishing purposes. It is also being used in aerosol propellants, anesthetics, the manufacture of plastics and refrigerants, the construction of buildings, and renovating them. According to the International Agency on Cancer Research (IARC), VCM is reported as a Group 1 carcinogen. Its high amounts of exposure to vinyl chloride, like 30,000 ppm, were a very high amount for rats. As a result, tumors arose from cymbal glands and then also developed Zymbal's gland carcinoma in rats. Pulmonary tumors and lesions were also observed in animals that developed Zymbal's carcinoma [24]. Three separate instances of hepatic angiosarcoma (HAS) were reported in Kentucky after an epidemiological survey in 1974. Through detailed investigation, it has been confirmed that vinyl chloride is the major cause of it. Due to this, the Occupational Safety and Health Administration (OSHA) passed laws that would help limit the use of VCM down to 1 ppm instead of 500 ppm, having a degree of activity of 0.5 ppm. After this standard protocol, zero cases of HAS have been reported in the US up until now [25].

Organic and Inorganic Brominated Chemicals

Various researchers have observed and reported that a number of brominated compounds, both organic and inorganic, can

cause cancer in animals. In the case of humans, these chemicals cause sterility issues, but no mortality has ever been reported up until now [26]. An epidemiological study was conducted among more than 10,000 people in the US. The data on their workplace hygiene were not available, but their cases were studied by their work-field relationship to know the chemicals to which they were exposed during their lifetime or by performing the drinking water test. It was observed that the workers exposedto DBP and trihalomethanes had an increased risk of bladder cancer [27]. Circulatory systemdiseases were caused by 1,2-dibromo-3-trichloro propane DBCP. Due to the lack of historical data, an exact estimate of deaths by specific chemicals was very difficult to calculate [28].

Mixed Halogenated Compounds

Dibenzo-p-dioxin and dibenzofuran are environmental pollutants commonly found in groundwater through aqueous chlorination and in air through combustion, automobile, chemical, and industrial waste gases. Dibenzofuran is also found in cigarette ashes and is also a by-product of the pharma industry [29]. Both of them can be formed in the environment or the laboratory. Municipal waste incineration is the source of their release into the environment. These processes take place in excess of chlorine. The use of these chemicals is banned in many countries. Sometimes the substitute for these chemicals is also present in automobile exhausts, so it is also considered a source. Gasoline additives were present in fuels. The effects of these chemicals on animals were studied by conducting laboratory studies, and it was concluded that both of these chemicals are responsible for hypothyroidism, lethality, waste, loss of body mass, and thymic atrophy [30, 31].

Treatments

Photodynamic treatment (PDT)

Light, O2, and a photosensitive agent are the three primary components needed for the PDT method [32]. In recent times, dynamic therapies have gained significant attention as a promising therapeutic approach for cancer treatment. This is primarily due to their enhanced disease specificity compared to conventional chemotherapy methods. Dynamic therapies rely on the activation of external stimuli, such as light, ultrasound, magnetic fields, electricity, ionizing

irradiation, or the utilization of endogenous chemicals like hydrogen peroxide (H2O2). These stimuli induce the generation of various reactive species, including reactive oxygen species (ROS) [33]. The mechanism of action can be conceptualized as the initiation of cellular apoptosis or necrosis through the degradation of cellular constituents, including proteins, lipids, or nucleic acids [34]. Problems with selection, poor solubility in water, possible detrimental impacts on normal tissues, and skin light sensitivity connected to specific PSs could render it challenging for PDT procedures to be used clinically. To address these difficulties, numerous research teams have been formed, and throughout

recent years, numerous encouraging targeted approaches have been published [35]. New strategies are being developed to increase the effectiveness, accuracy, and accessibility of PSs to tumor tissues.

The initial medication/device combination which the FDA authorized was PDT. According to Agostinis et al., PDT was the initial medication/device combination which the FDA had authorized. Thus far, several PSs have been developed and made available for purchase or employed in research studies [36]. Photofrin (porfimer sodium) constitutes one of the PSs that is most regularly utilized within the medical setting. In 1993, Canada grantedthe initial authorization of PDT using Photofrin as a therapy for urethral carcinoma [37]. In Germany, photofrin had been initially authorized for treating the earlier stages of pulmonary carcinoma. Nevertheless, it was allowed for managing aggressive respiratory malignanciesin other parts of Europe [37]. As a result, the FDA has granted approval for Photofrin for three uses, which include the management of micro-invasive endobronchial non-small-cell lung cancer (NSCLC), the alleviation of symptoms for individuals entirely as well as incompletely impeding NSCLC, along with surgically removing advanced dysplasia in Barrett's oesophagus. A few PSs which were granted

FDA approval are shown in Table 1. It is typically activated upon illumination by a red-coloured laser beam. The Food and Drug Authority (FDA) has recently authorized.

Table 1: Recognized photosensitive agents that have been authorized by the FDA for

treatmentof various cancers [37].

Photosensitive agent	General guidelines and therapeutic applications
Porfimer sodium	Alleviation of gastroesophageal carcinoma victims
	Individuals having fully or partially obstructive endobronchial NSCLC

Table 2: Clinical Applications of HIFU intreating different subcategories of cancers

	can receive therapy for micro-invasive endobronchial NSCLC, as well as measures to lessen blockage and relieve discomfort.
	For treatment of complex abnormalities associated with Barrett's oesophagus
Aminolevulinic acid	Dermal remedy for actinic keratoses that are thin to medium in thickness on the face, the head, or upper limbs
	Individuals having gliomas are advised to use the oral solution as a visualizing reagent as an adjuvant for the observation of aggressive cancer cells during operation
Methyl aminolevulinate	Management of immunodeficient individuals' light and fairly dense actinic keratoses on their faces and heads that are not hyperkeratotic or pigmented
Hexaminolevulinate	An imaging reagent recommended for usage in cystoscopic diagnosisof bladder cancer

Aminolevulinic acid (ALA) to be utilized as a topical remedy for actinic keratoses on the face, scalp, or upper limbs which are slight to considerably thick (summarized in Table 1).

Furthermore, the FDA has authorized the administration of ALA dietary treatment for individuals diagnosed with glial cell tumours as an adjuvant, which aids in enabling the detection of cancerous cells in surgery

(summarized)(Table 1) [38]. According to a recent study, the utilisation of DL-PDT in conjunction with physical approaches yielded superior clinical and histopathological outcomes. The AK-clearance rates showed a statistically significant increase at both the 1-month and 3-month intervals following treatments with a CO2 laser. The effects of photo-rejuvenation were found to be more pronounced when pretreated with CO2 laser and microdermabrasion. The application of pretreatment with a CO2 laser resulted in a notable decrease in

solar elastosis and an increase in collagen type 1. The findings of this study indicated that pre-treatment with laser may be a more favourable choice for managing skin field cancerization on the face [39]. A separate investigation was conducted to evaluate the impact of photodynamic diagnostics (PDD) utilising hexaminolevulinate on the diagnostic and therapeutic results among individuals with nonmuscle invasive bladder cancer (NMIBC). The study conducted by the researchers revealed that the utilisation of photodynamic diagnosis (PDD) in combination with white light cystoscopy (WLC) leads to the detection of a considerably higher number of tumours compared to the use of WLC alone. The enhanced diagnostic capabilities of PDD have been found to result in notably reduced rates of short-term recurrence following transurethral resection, potentially leading to improved treatment outcomes for patients with non-muscle invasive bladder cancer (NMIBC) [40].

Multikinase inhibitors

Recent research studies have demonstrated the efficacy of novel multikinase inhibitors and selective inhibitors in the management of medullary thyroid cancer, radioiodine-refractory thyroid cancer, and anaplastic thyroid cancer. These therapeutic interventions have shown promising results in terms of enhancing progression-free

overall survival. Numerous medical practitioners' express apprehension over the dose-limiting negative reactions associated with such medications and exhibit caution

when commencing therapy in individuals who exhibit systemic wellness but possess a substantial amount of disease burden. Consequently, determining the appropriate moment for treatment commencement becomes a complex task. The availability of mechanistic data on tyrosine kinase inhibitors (TKIs) in the literature has significantly contributed to enhancing our comprehension of optimal dosing strategies for these pharmaceutical agents. One of the primary objectives in the field of TKI therapy is to effectively block the activity of oncogenic kinase drivers, while simultaneously ensuring the preservation of patient quality of life. Published data on the real-world outcomes of tyrosine kinase inhibitors (TKIs) are increasingly available, providing insights into their performance outside the controlled setting of clinical trials. This review aims to present a comprehensive overview of the existing literature about the effectiveness of tyrosine kinase inhibitors (TKIs) in real-world clinical settings. The objective is to offer healthcare professionals a more accurate understanding of the practical outcomes and patient experiences associated with TKI therapy. In addition, researchers examined the available data about the mechanisms of inhibition, results, and adverse effects associated with tyrosine kinase inhibitors (TKIs). Additionally, we present a current overview of the targeted therapeutic approaches for thyroid cancer, with a specific emphasis on the optimization of treatment initiation timing [41, 42].

High intensity focused ultrasounds (HIFU) as a therapeutic strategy against solid cancers

Thermal tumor ablation techniques, such as radiofrequency, microwave, LASER, high-intensity focused ultrasound, and cryoablation, are commonly employed in the clinical setting for the treatment of liver, kidney, bone, or lung tumors. Nevertheless, it is important to note that the aforementioned procedures are mostly reliant on thermal energy and, as a result, they may be susceptible to the heat sink effect. This phenomenon might potentially hinder the complete ablation of targeted tissues, and there is also a risk of thermal damage occurring in non-targeted tissues. Under specific circumstances, the application of a high voltage pulsed electric field has the potential to initiate the creation of holes

within the cellular membrane. The scientific term for this occurrence is electropermeabilization, which is commonly referred to as "electroporation". Under specific circumstances,
electroporation may result in an irreversible state, ultimately culminating in cellular demise. The efficacy of irreversible electroporation has been proven in the treatment of liver and prostate cancers, although there isless data available regarding its effectiveness in treating pancreatic and kidney tumors. In the context of reversible electroporation, the temporary permeability of cells can be used to facilitate the introduction of cytotoxic medicines into tumor cells, with bleomycin or cisplatin being typically employed for this purpose. The utilization of reversible electroporation in combination with cytotoxic medicines exhibits potential in terms of oncological response, notably for solid cutaneous and subcutaneous tumors such as melanoma. Both irreversible and reversible electroporation is non-thermal ablation procedures, which offer a promising avenue for tumor ablation [43].

Chemotherapy Mediated by Nano Drug Delivery Systems

To carry therapeutic medicines to tumor cells, transition metals are thought to be effective nanocarriers. It is particularly intriguing for such types of substances because theycan function as nanocarriers as well as have photosensitizing capacity. A recent study investigated the lethal impact of the chemotherapy drug daunorubicin on leukaemia tumor cells. The research examined the effects of both the lack and presence of ZnO
nanoparticles of varying sizes. The researchers employed fluorescent microscopy, UV-Vis absorption spectroscopy, electrochemical examination, and the MTT test to analyze the outcomes. In this study, researchers additionally examined the impact of various sizes of zinc oxide nanoparticles on the cytotoxic reduction of daunorubicin in leukaemia tumor cells. The findings suggest that the concurrent use of nanoparticles made of zinc oxide of varying sizes and daunorubicin, when exposed to UV light, may exhibit an advantageous lethal

Sr. No	Type of Cancer	Clinical Study	Result	References
1	**Prostate Cancer**	The investigation focused on oncological follow-up and safety data pertaining to the utilization of focal high-intensity focused ultrasound (HIFU) treatment.	One year after HIFU treatment, histological examination revealed the presence of prostate cancer (PCa) in 13 out of 29 individuals, accounting for 44.8% of the cohort. Two years after HIFU treatment, an additional 24.1% patients were diagnosedPCa.	[44]
2	**Breast Cancer**	The study centered on examining the immunological response occurring in tumor-draining lymph nodes (TDLNs) following HIFU therapy	The group that underwent HIFU treatment exhibited a greater occurrence of immunological reactions in the axillary lymph nodes (ALNs) in comparison to the control group (100% versus 64%). Among the group of individuals with ALNs, 78.3% displayed a concurrent cellular and humoral immune response compared to only 36% of the control group.	[45]
3	**Liver Cancer**	The efficacy of trans-arterial chemo-embolization (TACE)in comparison with a high intensity focused ultrasound (HIFU) was assessed inrelation to TACEmonotherapy in a cohort of individuals diagnosed withprimary liver cancer.	At the 6-month follow-up period, the observation group exhibited a statistically significant decrease in Alpha-fetoprotein levels compared to the control group. The combination of TACE with HIFU for the management of primary liver cancer exhibits a superior overall remission rate,minimal harm to healthy liver tissue, complete eradication of tumor cells, and a reduction in postoperative local recurrence and metastasis rates, all while minimizing side responses.	[46]
4	**Renal Carcinoma**	This study aimed to evaluate the efficacy and safety of combining High-Intensity Focused Ultrasound (HIFU) with Transarterial Chemoembolization (TACE) in the treatment of liver	In the cohort comprising both groups, the observed 1-year survival rate was 100%, the 3-year survival rate was 84.0%, and the 5- year survival rate was 16.0%. Conversely,the comparator group exhibited survival ratesof 82%, 16%, and 0% for the corresponding time intervals.	[47]

		function impairment and immune function in paediatric patients with hepatoblastoma (HB).		
5	**PancreaticCancer**	In those suffering from malignant biliary obstruction (MBO) brought on by pancreatic carcinoma (PC), this research sought to assess the therapeutic efficacy of stent implantation alongsidehigh intensity-focused ultrasound ablation(HIFUA).	The percentage of stent implantation accuracy was discovered to be 100%. A collection of 26, 18, and two participants underwent 2, 3, and 4 rounds of HIFUA in the combination therapy cohort. 82.6% individuals that received HIFUA therapy exhibited a favorable medical result. In the combined category, 9 individuals experienced stent malfunction, compared to 15 individuals who were in the stent-onlycohort. For the combined group, the average duration of stent integrity was 188 days, compared to a duration of 4 months within the stent-only cohort.	[48]

impact on leukaemia tumor cells. This implies that zinc oxide nanoparticles hold significant promise for therapeutic and biological uses, as demonstrated by the outcomes [49]. A separate investigation documented the use of drug-loaded ultra-small Cu2-xSe theranostic nanoparticles (NPs) for the management of orthotopic aggressive glioblastoma by imaging-guided second near-infrared (NIR-II) PDT and chemotherapeutics. The ultra-small Cu2-xSe nanoparticles exhibit a significant level of absorbance in the near-infrared (NIR-II) range, with their sensitivity at 1064 nm being approximately twice as high as that at 808 nm. The high sensitivity of near-infrared II (NIR-II) and the enhanced ability of NIR-II light to penetrate deeper layers of tissue contribute to the exceptional effectiveness of PDT when exposed to a 1064 nm laser. Furthermore, it was shown that ultra-small Cu2-xSe nanoparticles exhibit a significant capacity to generate high quantities of reactive oxygen species by both transferring electrons, leading to the production of hydroxyl radicals (˙OH), and transmission of energy, resulting in the synthesis of singlet oxygen (1O2), when subjected to radiation. Moreover, the transportation of such

nanoparticles (NPs) can be efficiently achieved within orthotopic malignant glioblastoma through the utilization of focused ultrasound. The Cu2-xSe nanoparticles that have been produced hold potential for utilization in photoacoustic imaging, enabling the guidance of a combined approach involving near-infrared (NIR-II) PDT and chemotherapy. The findings indicate a substantial inhibition of tumor development. This studyshowcases the considerable possibility of drug-loaded ultra-small Cu2-xSe nanoparticles as a highly prospective therapy for the management of orthotopic aggressive glioblastoma [50].

Conclusion

All investigations and facts presented above lead us to the conclusion that cancer is a rising issue in the modern day and that it is influenced by exposure to many chemicals, of which we have spoken in length about halogenated substances. The effects of varioushalogenated compounds on different body parts depend on their characteristics, and the length and frequency of exposure to a given carcinogenic compound determines whether cancer develops. However, other methods are available for treating cancer, such as chemotherapy, surgery, high-frequency ultrasounds, and others. There are varied success rates, therefore it's important to keep in mind that treating and curing cancer isn't alwayachievable. Whether a safe dosage level exists for these chemicals is another crucial query that remains unresolved. Although the precise answer to this question is uncertain, it is nevertheless possible to state that the longer the exposure, the higher the likelihood that an individual would get any sort of cancer.

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