AITOX 에이아이탁스
Nonclinical Consulting

Weight-of-Evidence Assessment of the Carcinogenicity and Chronic Toxicity of Test article

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SUMMARY

● Safety concerns exist regarding Test Article. This is because carcinogenicity testing and chronic toxicity testing have not been performed on the test article. To overcome this, a weight-of-evidence assessment was conducted based on the biocompatibility data for Test Article and its original [redacted], Parent-compound. This assessment confirmed that Test Article is non-carcinogenic and predicted that it would not exhibit chronic toxicity.

● Understanding the degradation products of Test Article is more important than using a weight-of-evidence approach based on biocompatibility data to demonstrate its non-carcinogenicity and lack of chronic toxicity. Test Article is a Raw-material [redacted] that degrades into degradation products via hydrolysis. In general, it is accepted that chemical carcinogenesis begins with a primary mutation in a normal cell. Mutations arise from either electrophilic metabolites generated by enzymatic catalytic reactions catalyzed by cytochrome P450 or from electrophilic degradation products resulting from non-enzymatic natural decomposition, such as hydrolysis. That is, DNA damage leading to mutations occurs through covalent bonding between electrophilic metabolites or electrophilic degradation products and the nucleophilic sites of DNA bases. Numerous studies to date have confirmed that Raw-material does not convert to electrophilic degradation products via hydrolysis. This is supported by the negative results in the Test Article genetic toxicity test. Furthermore, most chronic and acute toxicity from chemical exposure arises from toxic mechanisms such as enzyme activity inhibition and oxidative stress caused by covalent bonding between electrophilic metabolites and electrophilic degradation products with lipids, proteins, and sugars, including nucleic acids that constitute cells. Considering these facts, it is natural that no toxicological changes were observed in all biocompatibility tests for Test Article. This fact is consistent with the absence of any toxicological changes observed in the biocompatibility tests of Parent-compound, the raw material of Test Article before its physical modification.

● **Therefore, the fact that Test Article does not convert to electrophilic species constitutes the most critical inference for weight−of−evidence assessment in predicting non−carcinogenicity and no chronic toxicity.**

STATEMENT REGARDING THE REPORT

This report assessed the noncarcinogenicity and chronic toxicity of Test Article using a non-experimental weight-of-evidence approach. The data used for the evaluation included biocompatibility data for Test Article and its original thread, Parent-compound, as well as other research materials, and the assessment was conducted truthfully. Furthermore, it is stated that permission to use the data for the preparation of this report was granted by AITOX Biopharmaceuticals Inc., the manufacturer of Parent-compound.

Report written by  [redacted]

Yeong-Chul Park Ph.D. in Toxicology Date

Certification of Review Quality

Part I. Weight-of-evidence assessment for demonstrating the non-carcinogenicity of Test Article

1. Objectives

● No carcinogenicity data was submitted among the biocompatibility items required for the development of the medical device Test Article, which is the subject of the test. To address this issue, the objective is to utilize the S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals, adopted as Guidance for Industry by the U.S. Food and Drug Administration (FDA) in 2022, as described in <BOX-1>. The guidance document and integrated addendum detail an integrative, weight-of-evidence (WoE) method of determining whether carcinogenicity testing in rats will be informative in human risk assessments for drug approvals. However, the final finished device requiring review is not a pharmaceutical. Nevertheless, since the FDA requested the submission of information on carcinogenicity and chronic toxicity based on chemical properties, the test article within 'Absorbable Raw-material chemicals with point' becomes Raw-material chemical called as Test Article. The S1B(R1) Addendum guidance establishes non-carcinogenicity for new drugs by providing justification for the '5 factors to consider for a weight-of-evidence assessment'. For the test article Test Article in the report, non-carcinogenic potential was demonstrated by providing justification and explanations for the five weight-of-evidence factors. This was achieved using results from conducted biocompatibility tests and leveraging public sources.

<BOX-1> S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals
A. Factors to Consider for a WoE Assessment (2.1): A WoE approach is based on a comprehensive assessment of the totality of data relevant to carcinogenic potential available from public sources and from relevant drug development studies. These factors include, but are not limited to: **Factor-1:** Data that inform carcinogenic potential based on drug target biology and the primary pharmacologic mechanism of the parent compound and major human metabolites; this includes drug target distribution in rats and humans along with the pharmacologic activity and potency of the parent compound and major metabolites in these species; available information from genetically engineered models; human genetic association studies; cancer gene databases; and carcinogenicity information on class effects, if available. **Factor-2:** Results from secondary pharmacology screens for the parent compound and major

metabolites that inform selectivity and off-target potential, especially those that inform carcinogenic risk (e.g., binding to nuclear receptors) histopathology data from repeated-dose toxicity studies completed with the compound, with particular emphasis on the 6-month rat study, including plasma exposure margin assessments of parent drug and major metabolites.

Factor-3: Evidence for hormonal perturbation, including knowledge of drug target and compensatory endocrine response mechanisms; weight, gross and microscopic changes in endocrine and reproductive organs from repeated-dose toxicity studies; and relevant results from reproductive toxicology studies, if available.

Factor-4: Genetic toxicology study data using criteria from ICH guidance for industry S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (June 2012); equivocal genotoxicity data that cannot be resolved in accordance with ICH S2(R1) recommendations increases uncertainty with respect to the carcinogenic potential

Factor-5: Evidence of immune modulation in accordance with ICH S8. Evidence of broad immunosuppression may provide sufficient concern for human risk that would not be further informed by standard rat and mouse carcinogenicity studies.

2. Demonstration of the non-carcinogenicity of test article 'Test Article' based on 5 WoE factors

2-1. Justification for Factor-1(Data that inform non-carcinogenic potential based on drug target biology and the primary pharmacologic mechanism of the parent compound and major human metabolites)

1) Target biology by the parent compound

1-1) The results of the 30-week subcutaneous implantation test submitted to the FDA: Almost all drugs have targets within the body and exert pharmacological or toxic effects through their action on these targets. However, Test Article or absorbable Raw-material chemical, which is part of the final medical device, has no target organ or target receptor. These materials are simply absorbable chemicals that, after closing surgical wounds, naturally degrade and are absorbed within the animal body over a certain period. Thus, the absence of pharmacologic effects of Test Article in animals can be confirmed through the results of the 30-week subcutaneous implantation test submitted to the FDA as shown in <Box 2>.

[redacted]

This study was performed to evaluate local tissue response of chemical, a component of Test Article (AITOX-product), by subcutaneous implantation in Sprague-Dawley rats for 1, 4, 8, or 30 weeks. The chemical of the test article, Test Article (AITOX-product), and the chemical of the control article, [redacted] were subcutaneously implanted into 6 males per group, and assessment included mortality, clinical signs, and body weights for each group. Animals were euthanized after 1, 4, 8, or 30 weeks after implantation, and necropsy and histopathological examination were performed to evaluate biological response at the implantation sites.

1. [Mortality]

There were no mortalities.

2. [Clinical signs]

There were no implant sample-related effects.

3. [Body weights]

There were no implant sample-related effects.

4. [Necropsy finding]

The test sample and control sample at the implantation sites were observed at the end of the 1, 4, and 8-week observation periods, but they were not observed at the end of the 30-week implantation period. At the end of the 4-week and 8-week observation periods, the color of these samples had discolored and their sizes had decreased compared to before implantation.

5. [Histopathological examination]
After the test sample was implanted for 1, 4, 8, or 30 weeks, in histopathological examination, biological reaction at the test sample implantation sites and in surrounding tissue was calculated as 0.1, 0, 0, 0.5, respectively. At the end of the 30-week observation period, debris of the test sample or control sample were observed at most implantation sites. Based on the above results, under present experimental conditions, biological response after subcutaneous implantation of chemical, a component of Test Article (AITOX-product), for 1, 4, 8, or 30 weeks in Sprague-Dawley rats was 'minimal or no reaction.

1-2) Conclusions regarding target biology: Common pre-symptoms in carcinogenicity tests include changes in **cellular structure** [redacted]. These early indicators can help identify potential carcinogens before full-blown cancer develops. Here are some key pre-symptoms observed in cellular changes;

① Hyperplasia: the increase in the number of cells in a tissue or organ without tumor formation, a common preneoplastic response to stimulus

② Dysplasia: abnormal cell growth and organization, often a precursor to cancer.

● As in <BOX-3>, no hyperplasia or dysplasia - precancerous signs of carcinogenesis induced by Test Article - were observed over 30 weeks. According to research, as shown in Table 1, a rat's age of 30 months is equivalent to a human age of 75 years [redacted]. This indicates that a 30-week subcutaneous implantation of Test Article corresponds to a 75-year period in the human body, equivalent to a lifetime of implantation. **Therefore, it is judged that even if Test Article Test Article is implanted in humans throughout their lifetime, no carcinogenicity-related cellular changes will be observed. This indicates that Test Article Test Article lacks biological targets capable of inducing carcinogenicity.**

<BOX-3> Rat age versus human age: Social maturity phase [redacted]

2) Target biology by the degraded metabolites

2-1) Macrophage infiltration, and increased cellularity of macrophage: According to the pathological report in <BOX-4>, in the subcutaneous implantation study of Test Article in rats over 30 weeks, no difference was observed between the control group and the implanted group up to 8 weeks post-implantation. However, at 30 weeks, a significant amount of Test Article degradation occurred. No specific biological reactions other than degradation products and macrophage infiltration were observed at the implantation site. Macrophage infiltration was confirmed by Raw-material chemical implantation, regardless of biodegradability or non-biodegradability, due to either Raw-material itself or its degradation products [redacted] Therefore, the degradation products generated during the 30-week implantation test of Test Article are presumed to induce macrophage infiltration; however, this is a common biological response observed in other tests as well. Consequently, degradation products and the resulting macrophage infiltration were confirmed through the 30-week implantation of Test Article. However, **this** is a general phenomenon observed in most implantation tests and is not a target biological effect specific to Test Article. [redacted]

2-2) Conclusion: Specifically, 30 weeks of rat age corresponds to 75 years of human age. For the macrophage infiltration induced by the 75-year Test Tread transplant to influence carcinogenicity, the genotoxicity of Test Tread must be a prerequisite. This is because the harmful reactive oxygen species generated in macrophages induce the proliferation of initiated cells harboring genetic mutations [redacted] **And Test Article, the degradation mechanism** [redacted] **and its non-genotoxic nature were explained in sections 3-4. Justification for Factor-4's genotoxicity discussion.**

<BOX-4> Discussion and Conclusions from Pathological report - 'Subcutaneous Implantation Study of Test Article (AITOX-product) in Sprague-Dawley Rats<Study Number [redacted]
This study was performed to evaluate local effects of chemical, a component of Test Article (AITOX-product), in Sprague-Dawley rats after subcutaneous implantation. In results of histophathological examination, the biological response of the test sample in the implanttion response evaluation about implant site was minimal or no reaction across all in implantation peridos. In the implantation sites of the test and control sample, a decreasing trend in cell type/tissue response was observed from implantation week 1 (G1) to implantation week 30 (G4). A similar level of response was also noted between the control sample and tissue in each group, leading to the conclusion of minimal or no reaction in the biological response assessmnet.

Until implantation week 8 (G3), both the test and control samples remained largely intact. However, by implantation week 30 (G4), [redacted]

Based on these results, when the chemical, a component of Test Article (AITOX-product), was implanted in Sprague-Dawley rats for subcutaneous implantation, the biological response to the test sample was minimal or no reaction.

3-2. Justification for Factor-2 (Results from **secondary pharmacology screens for the parent compound and major metabolites** that inform selectivity and off-target potential, especially those that inform carcinogenic risk (e.g., binding to nuclear receptors) histopathology data from repeated-dose toxicity studies completed with the compound, with particular emphasis on the 6-month rat study, including plasma exposure margin assessments of parent drug and major metabolites)

1) Secondary pharmacology by the parent compound and major metabolites

1-1) Definition and importance: Primary pharmacology refers to the main therapeutic effects of a drug, while secondary pharmacology involves additional effects that may not be the primary purpose of the medication. Futhermore, secondary pharmacology screening of investigational small-molecule drugs for potentially adverse off-target activities has become standard practice in pharmaceutical research and development, and regulatory agencies are increasingly requesting data on activity against targets with recognized adverse effect relationships[redacted]

1-2) The scores of biological response parameters as secondary response: However, during the 30-week Test Article study, no distinct primary biological response was observed due to the parent compound or its metabolites, indicating no changes attributable to secondary pharmacology. If biological changes are interpreted from a toxicological perspective, the final biological response score assessed after 30 weeks can be explained by secondary pharmacology. As shown in <BOX-5>, the biological response was judged to be 'minimal or no reaction' following the 30-week implantation of Test Article. This result indicates that even if a primary reaction occurs due to Test Article implantation, there is no secondary biological response or secondary pharmacology.

<BOX-5> Evaluation of local biological effects from the Final report - 'Subcutaneous Implantation Study of Test Article (AITOX-product) in Sprague-Dawley Rats<Study Number: [redacted]

● After the test sample was implanted for 1 week, 4 weeks, 8 weeks, or 30 weeks, in histopathological examination, **biological response at the test sample implantation sites and in surrounding tissue was calculated as '0.1', '0', '0', '0.5',** respectively. Based on the above results, under present experimental conditions, biological response after subcutaneous implantation of chemical, a component of Test Article (AITOX-product), for 1, 4, 8, or 30 weeks in Sprague-Dawley rats was **'minimal or no reaction.'**

● The scores of biological response parameters were totaled and then average scores for the test article and control article were calculated. The average score for the control samples was subtracted from the test samples average to determine a biological response grade according to the table below.

Score difference	Biological response
0.0-2.9	Minimal or no reaction
3.0-8.9	Slight reaction
9.0-15.0	Moderate reaction
>15.0	Severe reaction

2) Conclusion on the Carcinogenicity of Test Article Based on Secondary Pharmacology

● Drugs may exhibit secondary pharmacological responses beyond their intended therapeutic effects following the primary pharmacological response. These secondary pharmacological responses can be beneficial or may exert toxicological effects. Understanding how such toxicological responses arising from secondary pharmacological actions contribute to carcinogenesis is a core element of this topic. Specifically, although analysis of the parent compound and its degradation products was not performed, the co-existence of the parent compound and degradation products was confirmed. Furthermore, the 30-week subcutaneous implantation results for Test Article showed no significant biological response compared to the control group. **Consequently, no secondary pharmacological response was induced by Test Article, leading to the conclusion that it is not carcinogenic.**

3-3. Justification for Factor-3 (Evidence for hormonal perturbation, including knowledge of drug target and compensatory endocrine response mechanisms; weight, gross and microscopic changes in endocrine and reproductive organs from repeated-dose toxicity studies; and relevant results from reproductive toxicology studies, if available)

1) Hormonal perturbation and preneoplastic lesions

● Hormone-related cancers, namely breast, endometrium, ovary, prostate, testis, thyroid and osteosarcoma, share a unique mechanism of carcinogenesis. Endogenous and exogenous hormones drive cell proliferation, and thus the opportunity for the accumulation of random genetic errors [redacted] In other words, cells harboring mutant genes may undergo proliferation and additional mutations due to hormonal perturbation, potentially transforming into cancer cells. **In nonclinical studies, signs of hormonal perturbation by a drug are identified through indicators such as body weight, endocrine organ weights, and preneoplastic lesions assessed in subchronic toxicity studies**[redacted]

2) Subchronic (13-week) systemic toxicity study for Test Article

● <BOX-6> presents results related to hormonal perturbation indicators summarized from the 13-week systemic toxicity study of Test Article using rats. Key indicators include changes in body weight and hormone-related organs, as well as alterations observed macroscopically and microscopically. No effects attributable to Test Article were identified in the changes observed for these indicators. In addition, hematological tests, clinical biochemistry tests, organ weights, necropsy findings, and histopathological examinations were assessed, but no changes differing from the control group were observed. **Therefore, based on the Subchronic (13-week) systemic toxicity study, hormonal perturbation by Test Article is considered absent.**

<BOX-6> Indicators for hormonal perturbation from the final report: Subchronic Systemic Toxicity Study of Test Article (AITOX-product) by Subcutaneous Implantation in Sprague-Dawley Rats[redacted]	
Indicators for hormonal perturbation	**Results**
Body weight	Decreased body weight and body weight gain in both sexes were observed during the observation period in the test sample implantation group. **However, the changes were not considered adverse since body weight differences were within 6.3 % compared**

		to the negative control sample implantation group and values were within the range of Historical Control Data.
Gross and microscopic changes		**Granulomatous inflammation in implantation site was observed in all animals in the negative control sample implantation group and the test sample implantation group.** It is known that granulomatous inflammation could be caused by implantation of foreign material. Therefore, it was considered due to both implanted samples. In the test sample implantation group, severity of the lesion increased and, unlike the fibrotic pattern observed in the negative control sample implantation group, an ongoing inflammatory response was evident. However, the change was presumed to be due to the difference in absorbability between the negative control sample and the test sample. Additionally, the granulomatous inflammation remained localized around the implanted samples and was not accompanied by inflammation-related clinical pathology changes. Therefore, the change was not considered adverse.
Organ weight	Prostate gland	Absolute and relative weights of prostate gland significantly decreased (P<0.05) in males in the test sample implantation group. **However, the changes were not considered test sample-related since they were relative changes caused by increased weight in three males in the negative control sample implantation group considering enlarged prostate gland observed at necropsy.**
	Kideney	Terminal body weight showed a decreased tendency in both sexes in the test sample implantation group. Additionally, absolute weights of both kidneys significantly decreased (P<0.05) in males in the test sample implantation group. However, the above changes were not considered test sample-related **since there were no test sample-related changes in kidneys at histopathological examination and values were within the range of HCD(Historical Control Data).**

3-4. Justification for Factor-4 (Genetic toxicology study data using criteria from ICH guidance for industry S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (June 2012); equivocal genotoxicity data that cannot be resolved in accordance with ICH S2(R1) recommendations increases uncertainty with respect to the carcinogenic potential)

1) Chemical carcinogenesis and electrophilic properties

● As shown in Appendix 1 (Chemical Carcinogenesis and Chemical Properties), the carcinogenic process induced by chemicals and the characteristics of the chemicals that induce it have been summarized. This can be briefly summarized as having the following three characteristics:

① **Chemical carcinogenesis and Multistage-carcinogenesis:** The major stages of

chemical carcinogenesis have been deduced over the past similar to 50 years, primarily from animal model studies (and particularly from studies using the mouse skin model); these stages, called as multistage-carcinogenesis are termed initiation, promotion, and progression [redacted]

② Reactive intermetabolite by cytochrome P450-dependent activation reactions: The process of chemical carcinogenesis is extremely complex but can be depicted simplistically. In general, chemical carcinogens (pro-carcinogens), subsequent to their entry into the body, undergo biotranformation or metabolism [redacted]. Phase I metabolic reactions, catalyzed predominantly by the cytochrome P450 enzymes, can be characterized as reactive intremeuadtes by activation reactions, while phase II enzymes generally catalyze the detoxication of reactive intermediates by glutathione conjugating them to water-soluble and excretable products. **Especially, a reactive intermediate or intermediate is a short-lived, high-energy, highly electrophilic molecule and form bonds with nucleophilic bases in DNA, resulting in DNA mutation and cancer in order** [redacted]

③ Direct-acting electrophiles vs Indirect-acting electrophiles, inducing DNA Damage: Electrophiles are electron-seeking molecules that commonly form addition products, generally referred to as adducts, with cellular macromolecul, DNA. Some chemical carcinogens are direct-acting electrophiles, known as active electrophiles, in natural degradation processes such as hydrolysis. In contrast, the other substances, called reactive intermediates or metabolites, require biotransformation by enzymes in a process called metabolic activation. The latter are called indirect-acting electrophiles. **Therefore, substances that induce mutations in cells are procarcinogens that are either active electrophiles or reactive intermediates, acting through two pathways such as non-enzymatic or enzymatic processes, and are necessarily converted into electrophiles. The latter is called indirect-acting electrophiles** [redacted]

2) Chemical structure of Test Article and its degradation or biotransformation

2-1) Chemical Structure of Test Article: Test Article is a Raw-material chemical, as shown in <BOX-7>, and is primarily composed [redacted]

<BOX-7>

2-2) Degradation or biotransformation of Raw-material: The content from <BOX-8> to <BOX-11> is a research paper describing the degradation process of Raw-material. The common mechanism for in all papers is hydrolytic degradation. Hydrolysis is a non-enzymatic degradation method, meaning that Raw-material, a component of Test Article, **is not associated with biotransformation by cytochrome P450, etc.**

<BOX-8>

3) Degradation properties and electrophilic conversion of

3-1) Degradation properties or mechanism of [redacted] According to the content of <BOX-12> and <BOX-13> [redacted] **the degradation of Raw-material was presumed to occur in two stages.** The first stage of Raw-material degradation is hydrolysis via ester bond cleavage 10 weeks post-implantation, resulting in an increase in crystallinity, which are low molecular weight chain fragments. In the second stage, crystallinity undergoes degradation via heterogeneous mechanisms as the stress values of the chain fragments decrease due to external forces. **Therefore, whether these degradation products convert to electrophilic properties determines the presence or absence of genotoxicity, such as DNA damage leading to DNA adduct formation.**

[redacted]

3-2) Confirmation of the electrophilic properties of Raw-material degradation products

● As detailed in **<Appendix 1: Chemical Carcinogenesis and Chemical Properties>**, for a chemical to induce mutations primarily via DNA adducts, it must first undergo conversion to an electrophilic form. The electrophilicity of chemicals is achieved through two methods: non-enzymatic natural decomposition, such as hydrolysis, and biotransformation by cytochrome P450. Numerous studies have confirmed that Raw-material undergoes non-enzymatic degradation via hydrolysis. Therefore, it is necessary to verify whether the degradation products undergo conversion to electrophilicity.

● As shown in <BOX-14>, it was confirmed that hydrolysis increased more rapidly when Raw-material chemical was mixed with hyaluronic acid [redacted]. This promotion of Raw-material chemical hydrolysis by hyaluronic acid is possible because it exists as non-crosslinked, ultrafine particles, and both the Raw-material chemical and its degradation products are hydrophilic. Hyaluronic acid possesses the ability to attract and retain water up to 1000 times its own weight. Thus, the attractive force of hyaluronic acid induces degradation through hydrogen bonding with the hydrophilic Raw-material chemical, and the resulting degradation products are also hydrophilic, forming hydrogen bonds with hyaluronic acid. If the degradation products were electrophilic, they could not promote the hydrolysis of Raw-material chemicals by hyaluronic acid. This is because they cannot form hydrogen bonds with oxygen. **Thus, Raw-material chemical is highly hydrophilic, and its degradation products are also hydrophilic. This means that because the degradation products are not electrophilic, they do not induce mutations via DNA adducts. Based on this literature review, Raw-material chemical is determined to be non-carcinogenic.**

[redacted]

[redacted]

4) Results of the in vitro genetoxicity test for Test Article

4-1) Bacterial Reverse Mutation Assay with Test Article: <BOX-15> presents the results of the Bacterial Reverse Mutation Assay for Test Article conducted in accordance with the ISO 10993-3 guidunce (2014). Raw-material, a constituent of Test Article, degrades through natural decomposition by hydrolysis. Therefore, no electrophilic conversion via biotransformation occurs in the in vitro system of the S9 fraction, including the cytochrome P450 system. Consequently, a negative mutation response to Raw-material administration was confirmed. Furthermore, although degradation products are generated via non-enzymatic hydrolysis in the in vitro system lacking the S9 fraction, a negative mutation response was also confirmed. As such, it has been confirmed that the extract of Test Article does not convert to electrophilic degradation products via hydrolysis, which is the key reason for its negative mutation results in genotoxicity tests. **Therefore, as shown in Appendix-1, Test Article does not induce genetic toxicity and thus cannot initiate normal cells into mutated cells, the first step in chemical carcinogenesis. Consequently, Test Article is not a carcinogen.**

[redacted]

[redacted]

Test strain	S9 mix	Dose (100 μL/plate)			
TA strains	+/-	Negative vehicle (polar solvent)	Test sample (polar solvent)	Negative vehicle (non-polar solvent)	Test sample (non-polar solvent)
WP2 *uvr*A	+/-	Negative vehicle (polar solvent)	Test sample (polar solvent)	Negative vehicle (non-polar solvent)	Test sample (non-polar solvent)

[redacted]

4-2) In Vitro Mammalian Cell Gene Mutation Test with Test Article: This test was also performed in accordance with ISO 10993-3 guidance (2014), as with the 'Bacterial Reverse Mutation Assay with Test Article'. As shown in <BOX-16>, Test Article exhibited a negative mutagenicity response in the in vitro test using Mouse Lymphoma, regardless of the presence or absence of the S9 fraction. **The fundamental reason for this negative response was explained in '5-1) Bacterial Reverse Mutation Assay with Test Article', and consequently, Test Article is non-carcinogenic.**

[redacted]

Treatment series	Metabolic activation	Treatment time - recovery time (hrs)	Dose			
1	+	3-21	Negative vehicle (Polar solvent)	Test sample (Polar solvent)	Negative vehicle (Non-polar solvent)	Test sample (Non-polar solvent)
2	-	3-21	Negative vehicle (Polar solvent)	Test sample (Polar solvent)	Negative vehicle (Non-polar solvent)	Test sample (Non-polar solvent)
3	-	24-0	Negative vehicle (Polar solvent)	Test sample (Polar solvent)	Negative vehicle (Non-polar solvent)	Test sample (Non-polar solvent)

Treatment series	Metabolic activation	Treatment time - recovery time (hrs)	Positive control and dose (μg/mL)
1	+	3-21	B[a]P 2
2	-	3-21	4NQO 0.2
3	-	24-0	4NQO 0.05

Rapidly growing cells were transferred to a bioreactor tube (1×10^7 cells) and a $75cm^2$ flask (5×10^6 cells).

[redacted]

3-5. Justification for Factor-5(Evidence of immune modulation in accordance with ICH S8. Evidence of broad immunosuppression may provide sufficient concern for human risk that would not be further informed by standard rat and mouse carcinogenicity studies)

● **The document 'Guidance for industry:** S8 Immunotoxicity Studies for Human Pharmaceuticals' document provides recommendations on non-clinical testing for immunotoxicity. The initial screen for potential immunotoxicity involves standard toxicity studies. The document presented a method for confirming the presence or absence of immunotoxicity based on five parameters, as outlined in <BOX-17>, using data obtained from standard toxicity studies involving rodents or non-rodents, including both early short-term studies and repeat-dose studies (FDA, 2006). To confirm the immunotoxicity of the Test article Test Tread, we analyzed the Acute Systemic Toxicity Study and Subchronic Systemic Toxicity Study and reviewed five parameters. Consequently, no changes attributable to Test Article were observed in the two studies - the 'Acute Systemic Toxicity

Study in ICR mice' and the 'Subchronic Systemic Toxicity Study in Rats' - that evaluated these five immunotoxicity-related parameters.

<BOX-17> Findings and results from standard toxicity studies		
Parmeters	[redacted]	[redacted]
1. Hematological changes such as leukocytopenia , leukocytosis, granulocytopenia, granulocytosis, or lymphopenia, lymphocytosis	Data not available	Granulomatous inflammation in implantation site was observed in all animals in the negative control sample implantation group and the test sample implantation group. Additionally, the granulomatous inflammation remained localized around the implanted samples and was not accompanied by inflammationrelated clinical pathology changes. **Therefore, the change was not considered adverse.**
2. Alterations in immune system organ weights and/or histology (e.g., changes in thymus, spleen, lymph nodes, and/or bone marrow)	Data not available	Terminal body weight showed a decreased tendency in both sexes in the test sample implantation group. Additionally, absolute weights of both kidneys significantly decreased (P <0.05) in males in the test sample implantation group. However, the above changes were not considered test sample-related since there were no test sample-related changes in **kidneys** at histopathological examination and values were within the range of HCD(historical control data). Absolute and relative weights of **prostate gland** significantly decreased (P<0.05) in males in the test sample implantation group. However, the changes were not considered test sample-related since they were relative changes caused by increased weight in three males in the negative control sample implantation group considering **enlarged prostate gland** observed at necropsy. [redacted]
3. Changes in serum globulins that occur without a plausible	Data not available	**There was no change in the Albumin/Globulin ratio (A/G ratio) as determined by clinical biochemistry testing.**

explanation, such as effects on the liver or kidney, can be an indication that there are changes in serum immunoglobulins		
4. Increased incidence of infections	Not observed	Not observed
5. Increased occurrence of tumors can be viewed as a sign of immunosuppression in the absence of other plausible causes such as genotoxicity, hormonal effects, or liver enzyme induction	Not observed	Not observed

3. Conclusion on the non-carcinogenic potential of Test Article

● The following is a weight-of-evidence assessment justifying that Test Article is non-carcinogenic in two aspects.

① The non-carcinogenicity of chemical substances is not necessarily proven through carcinogenicity testing; it is demonstrated non-test-based methods using data from toxicity test data performed on the target chemical, and other relevant literature. Specifically, the FDA (2022) guideline 'S1B(R1) Testing for Carcinogenicity of Pharmaceuticals' presents methods for demonstrating non-carcinogenicity based on the 5 factors to consider for a weight-of-evidence assessment. The five weight-of-evidence factors, summarized as biological effects related to carcinogenesis, are: ① Target biology and the primary pharmacologic mechanism, ② The presence and effects of secondary pharmacology, ③ Hormonal perturbation, ④ Genotoxicity, and ⑤ Immunotoxicity. **Data for the weight-of-evidence assessment based on these five factors included biocompatibility tests such as the 30-Week Subcutaneous Implantation Study, the 13-week Subchronic Systemic Toxicity Study, the Acute Systemic Toxicity Study, and the Mutation Assay. In**

conclusion, this approach enabled a sufficient weight-of-evidence assessment to predict that Test Article is a non-carcinogenic substance.

② Of course, these five factors are not limited in terms of weight-of-evidence assessment for proving the non-carcinogenicity of Test Article. More importantly, as presented in <Appendix-1> Chemical Carcinogenesis and Chemical Properties, the transformation of the parent substance's metabolites or degradation products into chemically reactive properties is key. In most chemical carcinogenesis processes, the initiation involves a primary mutation in a normal cell. This mutation occurs when a chemically reactive metabolite or degradation product forms a covalent bond with a nucleophilic DNA base. The degradation products generated by the hydrolysis of Test Article were confirmed through a Mutation Assay not to convert into chemically reactive electrophilic species. Specifically, electrophilic metabolites and degradation products induce toxicity by covalently binding to nucleic acids and proteins, leading to enzyme inhibition, and by reacting with lipids to induce oxidative stress. However, no toxicological lesions or indicators of reactions with proteins or lipids were identified in any biocompatibility tests performed on Test Article. **Therefore, the fact that Test Article does not convert to electrophilic species constitutes the most critical inference for weight-of-evidence assessment in predicting non-carcinogenicity.**

Part II. Opinion on the Safety of Test Article Following Parent-compound's Physicochemical Treatment

1. Objectives

● Test Article is a Raw-material chemical developed through the physical modification of Parent-compound, a product of AITOX Biopharmaceuticals Corp. The physical modification of Parent-compound involves forming tiny barbs on the Raw-material chemical without any chemical modification. The test article, Test Article, is a monofilament barbed synthetic absorbable chemical. Tiny barbs are cut and bonded to the monofilament of Parent-compound to form the barbed chemical, Test Article. Since chemical characterization was not performed on Test Article, a comparison of its chemical properties with Parent-compound from a safety perspective is not possible. However, the safety of Test Article can be confirmed by comparing the biocompatibility tests performed on Parent-compound, the original chemical of Test Article. Therefore, the purpose of this discussion is to confirm the safety of Test Article through a comparison of biocompatibility tests.

2. Comparative Biocompatibility of Parent-compound and Test Article

● To assess safety, a comparison of the biocompatibility of Parent-compound and Test Article was conducted from the perspective of toxic endpoints, as shown in <BOX-16>. The toxic endpoint evaluation was performed through six toxicity tests as follows: ① Genotoxicity test, Intracutaneous Reactivity Test in Rabbits, ② Skin Sensitization Study in Hartley Guinea Pigs, ③ In vitro Cytotoxicity Test in BALB/3T3 cells, ④ An Acute Systemic Toxicity Study, ⑤ Subchronic Systemic Toxicity Study in Sprague-Dawley Rats, ⑥ Subcutaneous Implantation Study in Sprague-Dawley Rats. The tests were conducted according to OECD and ISO test guidelines based on GLP principles, and the toxicity testing methods for the two substances are identical. As shown in <BOX-16>, the two substances yielded nearly identical results in the six toxicity tests etc.

[redacted]			
Toxicity Endpoints	**Parent-compound**	**Test Article**	**Conclusive Prediction**

Genotoxicity test	**Bacterial Reverse Mutation Study**	The DMSO and saline test article extracts were considered to be **nonmutagenic** to S. typhimurium tester strains TA98, TA100, TA1535, and TA1537, and to E. coli tester strain WP2uvrA.	The results indicate that the test article, Test Article (AITOX-product), chemical, **was not mutagenic** in this bacterial assay system under present laboratory conditions and the result was clear negative.	Genotoxicity arises through the conversion of chemicals into electrophiles and their covalent bonding with DNA. Furthermore, most toxicity arises from interactions between the chemical's electrophilic nature and the body's constituent sugars, proteins, nucleic acids, and lipids. Therefore, the commonality between these two groups that do not induce genotoxicity is a critical endpoint that can predict the absence of toxicological positive responses in most biocompatibility tests.
	Mouse Lymphoma Assay	The RPMIo and DMSO test article extracts did not cause a 2-fold or greater increase in the mean mutant frequency of the L5178Y/TK+/' cell line either in the presence or absence of metabolic activation. The test article was **not mutagenic.**	The results indicate that the test article, Test Article (AITOX-product), chemical, **did not induce gene mutation** in Mouse Lymphoma L5178Y tk+/- cells in this assay system.	
Intracutaneous Reactivity Test in Rabbits		The test article met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean s**core was 0.0 and 0.0 for the SC and SO test article extracts, respectively.**	In evaluation of intracutaneous reaction, the average scores for t**he test sample site and the blank sample site (polar extraction vehicle) were all 0 and the final test score was also 0.**	In irritation tests, two substances were injected into rabbit paws but showed no irritant effects.
Skin Sensitization Study in Hartley Guinea Pigs		The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was **not considered a sensitizer** in the guinea pig maximization test..	It was considered that the sensitization potential of chemical, a component of Test Article (AITOX-product), **was 'Weak' (grade I).**	To assess skin sensitivity, both test substances were applied to guinea pigs, but the results were negative.
In vitro Cytotoxicity Test in BALB/3T3 cells		The test article extract showed **no evidence of causing cell lysis or toxicity.** The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity).	The test article, Test Article (AITOX-product) chemical, **did not induce cytotoxicity** in BALB/3T3 clone A31 cells in this assay system.	To assess cytotoxicity, both test substances were administered to cells but did not induce cell lysis or cytotoxicity.
An Acute Systemic Toxicity Study		There was **no mortality or evidence of systemic toxicity** from the extracts injected into mice. Each test article extract met the requirements of the	Based on the above results, after single dose intravenous or subcutaneous administration of extraction of cannula (point), a	Extracts from two chemical materials were confirmed to have no effect on

	study.	component of Test Article (AITOX-product) to ICR mice, **no mortalities were observed.**	mortality or systemic toxicity following acute administration.
Subchronic Systemic Toxicity Study in Sprague-Dawley Rats	There was **no microscpic and macroscopic evidence of systemic toxicity** following subcutaneous implatation of the test article (Parent-compound) for 26 weeks. The test article was considered a **non-reactive** when compared to the implanted negative control article(HDPE).	Subcutaneous implantation of the chemical from the test article Test Article (AITOX-product) in SpragueDawley rats for 90 days resulted in **no systemic toxicity and no target organ** was identified.	Parent-compound was evaluated for systemic toxicity for 26 weeks and Test Article for 13 weeks following subcutaneous implantation, but no systemic toxicity or target organs of toxicity were identified.
Subcutaneous Implantation Study in Sprague-Dawley Rats	The macroscopic reaction was not significant as compared to the comparator control article and **not significant as compared to the negative control article after 2, 16, and 30 weeks of implantation.** Microscopically, the test article caused a **minimal or no reaction as compared to the comparator control article** and a slight reaction as compared to the negative control article after 2. 16. and 30 weeks of implantation.	Biological response after subcutaneous implantation of chemical, a component of Test Article (AITOX-product), for 1, 4, 8, or 30 weeks in **Sprague-Dawley rats was 'minimal or no reaction.'**	During the 30-week subcutaneous implantation study, organized changes were observed at specific time points. Both substances were assessed as showing slight reaction, minimal reaction, or no reaction.

3. Conclusions

● Test Article is a chemical made of the same material as Parent-compound, featuring tiny barbs created through physical modification. That is, although physical changes occur, no chemical conversion takes place, so both chemicals are Raw-material chemicals. However, concerns about safety may arise due to the physical modification. **Due to these concerns, a comparative toxicity study involving six tests, including a genotoxicity test, was conducted on the two materials. The results confirmed the similarity in the absence of specific positive reactions in the toxicity tests for both materials.**

● This result indicates that both substances are composed of the same material, Raw-material. As explained in Part I on genetic toxicity, Raw-material undergoes hydrolysis, losing its electrophilic properties and gaining hydrophilicity. Electrophilicity causes toxicity by

forming covalent bonds with the four major macromolecules constituting cells: carbohydrates, proteins, lipids, and nucleic acids. **Therefore, the identical results indicating no specific toxicity through the toxicological endpoints of the two substances were confirmed. This is judged to be because the morphological changes did not induce chemical changes in the two substances.**

Part III. Opinion on the Chronic Toxicity of Test Article

1. Objectives

● The chronic system toxicity study provides information on possible health hazards likely to arise from repeated exposure over a considerable part of test species' lifespan. Studies provide data about toxic effects of a substance, indicate target organs and the possibility of accumulation. Test duration ranges from **26 to 52 weeks**, depending on test species. The majority of chronic toxicity studies are carried out in rodent species, but NHP are also used. However, a 26-week systemic toxicity test for Test Article, the test substance in this report, was not conducted. Therefore, the purpose of this report is to perform a weight-of-evidence approach to eliminate safety concerns arising from chronic exposure to Test Article.

2. Methods and Results for the weight-of-evidence assessment

2-1. Prediction of Chronic Toxicity Based on Results from a 30-Week Subcutaneous Implantation Study

● <BOX-17> shows the pathological findings following subcutaneous implantation of Test Article for 30 weeks, longer than the typical 26-week chronic toxicity period. Apart from the distribution of macrophages degrading the degradation products generated by the hydrolysis of the constituent Raw-material, the biological response to implantation was judged to be very minimal or absent. **Based on the results of this 30-Week Subcutaneous Implantation Study, it is concluded that Test Article exhibits negligible toxicity in chronic toxicity testing.**

[redacted]

Based on these results, when the chemical, a component of Test Article (AITOX-product), was implanted in Sprague-Dawley rats for subcutaneous implantation, the biological response to the test sample was minimal or no reaction.

2-2. Prediction of Chronic Toxicity through the 26-Week Subchronic Systemic Toxicity Study of Parent-compound, the Original chemical

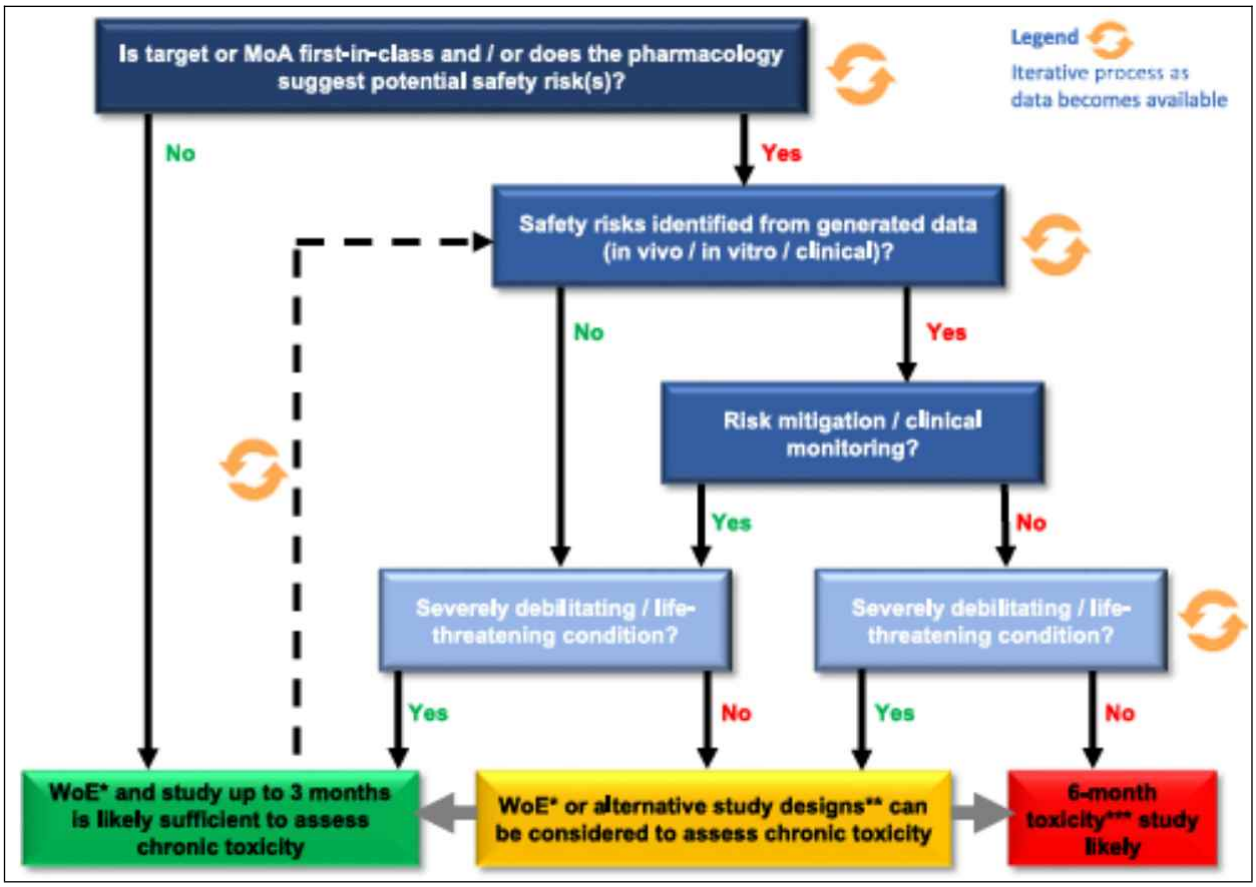
● Although non-toxic, Test Article underwent only a 13-week systemic toxicity study, not the longer 26-week systemic toxicity study, raising potential concerns about chronic toxicity. <BOX-18> presents the results of the 26-week systemic toxicity study for Parent-compound, the original chemical prior to the physical modification of Test Article. The results, obtained through subcutaneous implantation, showed no toxicity associated with Parent-compound compared to the control group. <BOX-16> shows the 'Comparison of Biocompatibility Between Parent-compound and Test Article in Terms of Toxic Endpoints'. Identical results confirming the absence of toxicity were observed for both materials in all biocompatibility parameters. Based on this evidence, the absence of chronic toxicity demonstrated for Parent-compound in the 26-week systemic toxicity study is extrapolated to Test Article, predicting it will also lack chronic toxicity.

<BOX-18> ISO Systemic Toxicology Study in Rats Following Subcutaneous Implantation, 26 Weeks

2-3. Prediction of Chronic Toxicity Based on Results from a 13-Week System

Toxicity Study

● BOX-18 is a model for determining whether to conduct a 26-week (6-month) chronic toxicity study for monoclonal antibodies (mAbs) based on the weight-of-evidence. The test article in this report is a synthetic polyoxanone polymer, which is not a biologic like monoclonal antibodies. However, given its lack of genotoxicity, the model can be used to determine whether a chronic toxicity study is necessary. This is because the first step of the ' weight-of-evidence approach' in the model - deciding whether to conduct a 13-week toxicity study instead of a 26-week chronic toxicity study - relates to the test article's pharmacological action being associated with a 'potential safety risk'. Title Content - Part 1. weight-of-evidence Assessment for Demonstrating the Noncarcinogenicity of Test Article' - It has been confirmed that Test Article does not induce 'targeted biology' or secondary pharmacology. Therefore, this corresponds to a 'No' answer to the first question in the decision tree of <BOX-18>, and for Test Article, it can be concluded that chronic toxicity prediction can be sufficiently achieved with a 13-week systemic toxicity study.



3. Conclusions

● A 26-week chronic toxicity study for Test Article was not conducted, and the weight-of-evidence assessment for this was based on ① the 30-Week Subcutaneous Implantation Study, ② the 26-week subchronic systemic toxicity study of Parent-compound, and ③ a model for determining whether to conduct a 26-week chronic toxicity study for monoclonal antibodies (mAbs) based on the weight-of-evidence. In conclusion, a weight-of-evidence assessment was performed based on these three data sets, which showed no evidence of toxicity. This assessment predicted that no toxicity would be observed in the 26-week chronic toxicity study for Test Article.

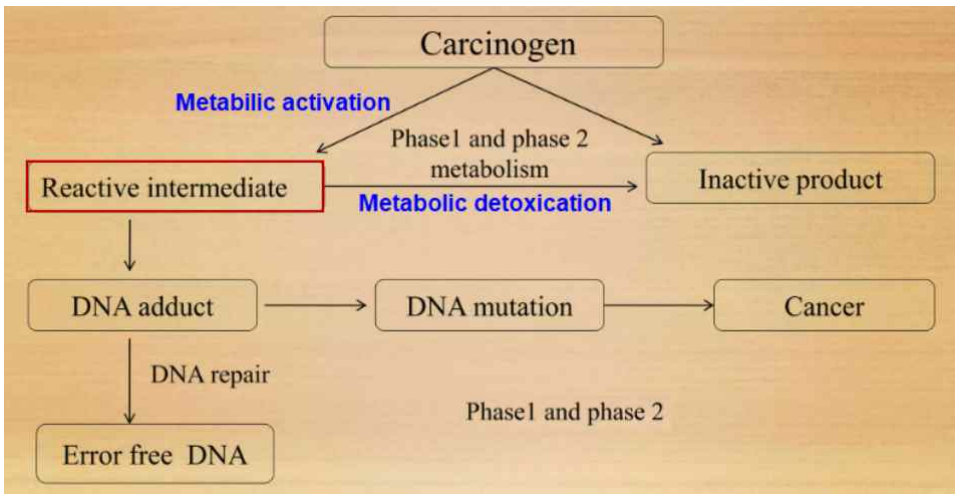
<Appendix-1> Chemical carcinogenesis and Chemical properties

1. Chemical carcinogenesis

1) Reactive intermetabolite by cytochrome P450-dependent activation reactions

● The process of chemical carcinogenesis is extremely complex but can be depicted simplistically as illustrated in Figure 1. In general, chemical carcinogens (pro-carcinogens), subsequent to their entry into the body, undergo metabolism[redacted]. Phase I metabolic reactions, catalyzed predominantly by the cytochrome P450 enzymes, **can be characterized as reactive intremeuadtes by activation reactions**, while phase II enzymes generally catalyze the detoxication of reactive intermediates by glutathione conjugating them to water-soluble and excretable products. Thus, it is evident that **a proper balance between the activating and detoxicating processes** is a critical determinant of the availability of reactive species and therefore, the ultimate carcinogenic potential of the chemical. In other words, increased availability of a reactive carcinogen, whether from **excessive exposure, activation, or too little detoxication may result in an elevated cancer risk.**

● **Especially, a reactive intermediate or intermediate is a short-lived, high-energy, highly electrophilic molecule and form bonds with nucleophilic bases in DNA, resulting in DNA mutation and cancer in order**[redacted]



<Figure 1> Mechanism of action on chemical cacinigenesis

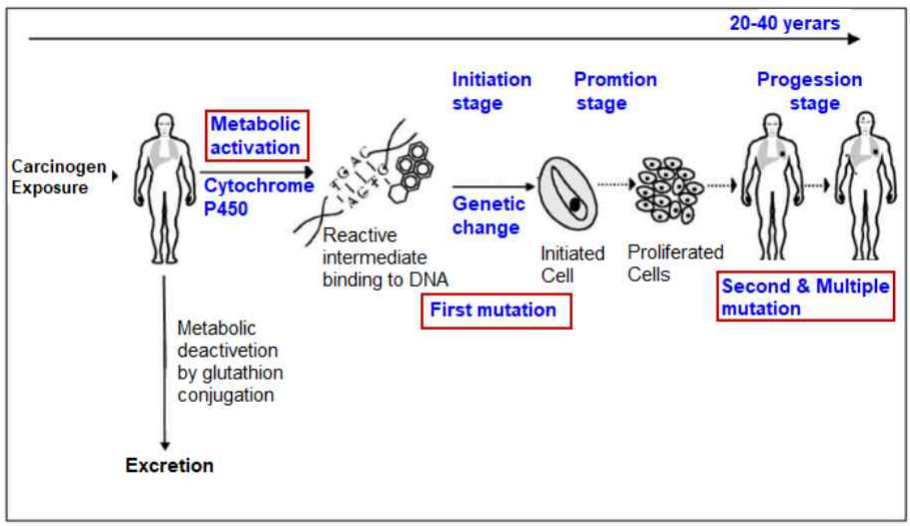
2) Multistage-carcinogenesis

● In shown in Figure 2. the major stages of chemical carcinogenesis have been deduced over the past similar to 50 years, primarily from animal model studies (and particularly from studies using the mouse skin model); these stages are termed **initiation, promotion, and progression**

● **Tumor initiation** begins when DNA in a cell or population of target cells is damaged by exposure to exogenous or endogenous carcinogens leading to mutations in critical target genes.

● **The tumor promotion stage** is characterized by selective clonal expansion of the initiated cells, a result of the altered expression of genes whose products are associated with hyperproliferation, tissue remodeling, and inflammation. During tumor progression, preneoplastic cells undergo malignant transformation through a process of selection that is facilitated by progressive genomic instability and altered gene expression.

● **During tumor progression**, preneoplastic cells undergo malignant transformation through a process of selection that is facilitated by progressive genomic instability and altered gene expression.



<Figure 2> Simplistic model of multistage carcinogenesis

● While the processes involved in each stage of experimental chemical carcinogenesis also appear to be involved in human carcinogenesis, the temporal nature of initiation, promotion, and progression events is more complex. In addition, multiple mutational events are

involved in the formation of human tumors. Genetic background and nutritional status can dramatically affect susceptibility to a carcinogenic exposure in both experimental animals and humans.

2. Chemical properties inducing DNA Damage

● Electrophiles are electron-seeking molecules that commonly form addition products, generally referred to as adducts, with cellular macromolecules including DNA, RNA, lipids, and proteins. Some chemical carcinogens are direct-acting electrophiles call as **active eletrophiles**, whereas others called as **reactive intermediates or metabolites** require biotransformation by enzymes in a process termed metabolic activation [redacted]

● Therefore, to induce the initiation stage of normal cells - the first step in the multistage theory of chemical carcinogenesis - a chemical must possess properties that induce DNA damage. A representative DNA damage caused by chemicals is a DNA adduct. DNA adducts form through covalent bonding between the nucleophilic site of a DNA base and the electrophilic site of the chemical. Within cells, chemicals are converted to electrophilic forms via two primary pathways: ① natural decomposition and ② biotransformation [redacted]

● As shown in Figure 3(Park et al., 2014), natural degradation is a method by which chemicals are converted into active electrophiles through processes such as hydrolysis without the aid of enzymes. In contrast, the process by which chemicals are converted into reactive metabolites - electrophilic metabolites - by enzymes such as cytochrome P450 is called biotransformation.

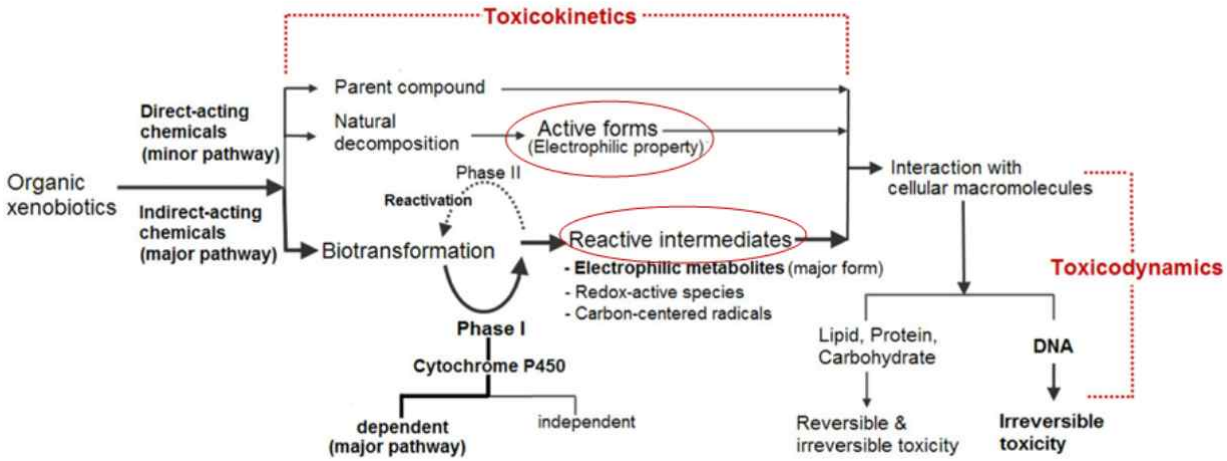


Figure 3. The simplest flowchart stating the mechanism for organic xenobiotics-induced toxicity

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